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Review

# Role of pattern recognition receptors in the development of MASLD and potential therapeutic applications

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ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) has become one of the most prevalent liver diseases worldwide, and its occurrence is strongly associated with obesity, insulin resistance (IR), genetics, and metabolic stress. Ranging from simple fatty liver to metabolic dysfunction-associated steatohepatitis (MASH), even to severe complications such as liver fibrosis and advanced cirrhosis or hepatocellular carcinoma, the underlying mechanisms of MASLD progression are complex and involve multiple cellular mediators and related signaling pathways. Pattern recognition receptors (PRRs) from ~~the~~ innate immune system, including Toll-like receptors (TLRs), C-type lectin receptors (CLRs), NOD-like receptors (NLRs), RIG-like receptors (RLRs), and DNA receptors, have been demonstrated to potentially contribute to the pathogenesis for MASLD. Their signaling pathways can induce inflammation, mediate oxidative stress, and affect the gut microbiota balance, ultimately resulting in hepatic steatosis, inflammatory injury and fibrosis. Here we review the available literature regarding the involvement of PRR-associated signals in the pathogenic and clinical features of MASLD, *in vitro* and in animal models of MASLD. We also discuss the emerging targets from PRRs for drug developments that involved

*Abbreviation:* MASLD, Metabolic dysfunction-associated steatotic liver disease; MASH, Metabolic dysfunction-associated steatohepatitis; HCC, Hepatocellular carcinoma; IR, Insulin resistance; T2DM, Type 2 diabetes mellitus; PRRs, Pattern recognition receptors; TLRs, Toll-like receptors; CLRs, C-type lectin receptors; NLRs, NOD-like receptors; RLRs, RIG-like receptors; PAMPs, Pathogen-associated molecular patterns; DAMPs, Damage-associated molecular patterns; LPS, lipopolysaccharide; PGN, peptidoglycan; LTA, Lipoteichoic acid; DsRNA, double-stranded RNA; HMGB1, High-mobility group box 1; ER, Endoplasmic reticulum; TIR, Toll and interleukin 1 receptor; IRAK, Interleukin 1 receptor-associated kinase; TRAF, Tumor necrosis factor receptor-associated factor; TAK1, transforming growth factor beta-activated kinase 1; TAB1, TAK1-binding proteins; NF-κB, NF-kappaB; MAPK, Mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; AMPK, AMP-activated protein kinase; AP-1, activator protein-1; TRIF, Toll/IL-1R domain-containing adaptor-inducing IFN-beta; TRAM, TRIF-related adapter molecule; TBK1, TRAF family member-associated NF-κB-binding kinase; IRF3, IKKi results in interferon regulatory factor 3; MD2, myeloid differentiation factor 2; MAMP, metabolism-associated molecular pattern; FFAs, Free fatty acids; Fetuin-A, Alfa 2-Heremans-Schmid; ENAMPT, extracellular nicotinamide phosphoribosyl transferase; HFD, High-fat diet; MCD, methionine/choline-deficient diet; CDAA, choline-deficient L-amino-acid; ROS, Reactive oxygen species; PAI-1, Plasminogen activator inhibitor-1; MPs, microplastics; GP, Gynostemma pentaphyllum; MtDNA, mitochondrial DNA; Poly I:C, polyinosinic-polycytidylic acid; LSECs, Liver sinusoidal endothelial cells; MDA, malondialdehyde; HemITAM, hemimmunoreceptor tyrosine-based activation; ITAM, Immunoreceptor tyrosine-based activation motif; Syk, Splenic tyrosine kinase; CARD9, Caspase recruitment domain-containing protein; Bcl10, B cell lymphoma/leukemia-10; LOX-1, Lectin-like oxidized low-density lipoprotein receptor-1; IRE1, Inositol-requiring enzyme 1, HLSECs, Human liver sinusoidal endothelial cells; PUFAs, Polyunsaturated fatty acids; NACHT, Nucleotide-binding and oligomerization structural domain; LRR, Leucine-rich repeat structural domain; NLRP, NLR family pyrin domain-containing protein; NOD, Nucleotide-binding oligomerization domain; LRR, Leucine-rich-repeat; CARD, Caspase activation and recruitment domain; MWS, Muckle-Wells syndrome; NIK, NF-κB-inducing kinase; RIG-I, Retinoic acid-inducible gene I; MDA5, melanoma differentiation-associated gene 5; MAVS, Mitochondrial antiviral signaling protein; CTD, C-terminal structural domain; VDAC2, Voltage-dependent anion channel 2; STING, Stimulator of interferon genes; CGAS, cyclic GMP-AMP synthase; CGAMP, cyclic GMP-AMP; EPS, Extracellular polysaccharides; PBMCs, Peripheral blood mononuclear cells; TNF-α, Tumor necrosis factor-α; IL-6, interleukin 6; IFN, interferon; CCL2, C-C motif ligand 2; FGF21, fibroblast growth factor 21; TGF-β1, Transforming growth factor beta1; TGF-α, Transforming growth factor; FasL, Fas ligand.

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agent therapies intended to arrest or reverse disease progression, thus enabling the refinement of therapeutic targets that can accelerate drug development.

## 1. Introduction

The prevalence of obesity has increased rapidly in most parts of the world over the past several decades, and this disease is closely associated with Type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, high blood pressure, sleep apnoea syndrome, and metabolic dysfunction-associated steatotic liver disease (MASLD) [1,2]. MASLD is now one of the leading causes of chronic liver disease. Studies have revealed that it is present of 17–33% of the global population, and it has become the primary cause of liver disease in many countries [3,4]. Particularly in patients with obesity, metabolic syndrome and T2DM, the prevalence of MASLD can be as high as 80%, of 20% of these patients may develop metabolic dysfunction-associated steatohepatitis (MASH) [5].

MASLD is typically characterized by excessive fat deposition in hepatocytes, and can range from milder forms steatosis to more severe forms such as MASH, advanced fibrosis, cirrhosis, hepatocellular carcinoma (HCC), and liver failure [4,6]. Although most patients with MASLD remain in a mild state, half of them may develop into MASH [7]. As obesity incidence increases globally, the prevalence of MASLD has becomes more severe, and one of the great challenges is that there is still a lack of effective medicines for preventing and treating MASLD clinically [8].

The pathogenesis of MASLD is not completely clear, and it is typically believed to be closely related to lipid metabolism disorders, insulin resistance (IR), oxidative stress, lipid peroxidation, inflammatory cytokines, and other factors. It has been observed that the interaction among the gut, liver, and immune system plays an important role in the development of MASLD [9,10]. The liver is the key frontline of the immune system. Ideally, when positioned to detect pathogens entering the body via the gut, the liver is designed to detect, capture, and clear bacteria, viruses, and macromolecules. The innate immune system in the liver is the first line of the body to recognize these microbes via pattern recognition receptors (PRRs) [11,12]. During MASLD development, gut flora-associated endotoxins and obesity-related metabolites trigger PRR-mediated signaling and inflammation, and a complex signal network in the liver is activated. Obesity-associated immune metabolic disorders, cellular innate immunity, altered microbial composition, and increased gut flora translocation will finally promote the development of chronic inflammation in the liver. In particular, the continued activation of immune signaling contributes to the development of MASLD into MASH [11].

In healthy mammalian livers, immune cells typically exhibit a resting or tolerogenic phenotype. However, during the progression of MASLD to MASH, danger signals and pro-inflammatory mediators released from damaged or dead hepatocytes alter the molecular profile of immune cells and liver parenchymal cells by activating PRRs involved in the pro-inflammatory phenotype [13,14]. PRRs and their related signaling pathways are associated with the development of many diseases, and how they determine the progression of MASLD is also a topic of interest in this field. PRRs are a large family that includs Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-like receptors (RLRs), C-type lectin receptors (CLRs), and DNA sensors [15,16]. The involvement of TLRs and NLRs has been described comprehensively, and some drugs-related TLR4, TLR9, and NLRP3 are being development and on the clinical trials [17,18]. The regulation of RLRs, CLRs and DNA sensors is the newly discoverer molecules that show their potential abilities as therapeutic targets. The cGAS-STING signaling in metabolic diseases has been indicated become a novel target option for pharmacotherapy [19]. In this manuscript, we comprehensively describe the emerging evidence of PRRs in the liver during the pathogenesis and progression of MASLD, their associated therapies that are currently under development, and possible future therapeutic options to combat MASLD.

## 2. PRRs

The concept of PRRs was first proposed by the immunologist Janeway [20], which refer to germline-encoded receptors that recognize pathogen-associated molecular patterns (PAMPs) from pathogenic microorganisms and damage-associated molecular patterns (DAMPs) from injured tissues, thus activating a series of signaling pathways to trigger the innate immune response [15]. PAMPs are typically exogenously conserved microbial products, such as lipopolysaccharide (LPS), peptidoglycan (PGN), bacterial DNA, and viral double-stranded RNA (dsRNA) that are important components for microorganism survival. DAMPs are primarily derived from the release endogenous products of damaged and/or dying cells, tissue damage debris, and energy metabolites [21]. Low levels of DAMPs induce physiological immune responses during tissue injury and facilitate the clearance of dead cells, whereas excessive levels of DAMPs such as high-mobility group box 1 (HMGB1), calreticulin, heat shock proteins, histones, and adenosine triphosphate can result in pathological condition.

The liver is a key-frontline immune tissue that is ideally positioned to detect PAMPs and DAMPs in the circulation and microenviroment against infection or injury by activating the PRR (Table 1) [11,22]. Caloric overconsumption promotes adipose and liver fat accumulation while perturbing the gut microbiome. Therefore, the accumulation of excess ingested lipids in the liver can result in hepatocytes blooming and damage, thus inducing DAMPs for PRRs detection to activate inflammatory signaling molecules and mediate hepatic inflammation that in turn leads to the development of MASLD [11]. Moreover, obesity-related metabolic disorders can lead to intestinal flora disorders, intestinal barrier shifts, and the accumulation of harmful bacteria, as DAMPs can enter the portal vein through the hepatic-intestinal axis and can be recognized by PRRs, ultimately leading to hepatic inflammation and cellular damage.

Once inflammation and fibrosis occur, it becomes difficult to reverse the disease progression [23]. The current MASLD treatment options and methods for preventing MASH progression remain limited. Targeting PRR can alleviate MASLD, and the use of these receptors to inhibit MASLD development is a hot research topic in this field. Here, we describe the location, function, signaling, and potential treatments associated with each type of PRR in the pathogenesis and progression of MASLD.

## 3. TLRs

TLRs are among the earliest discovered germline-encoded PRRs, with a specific genetically determined number in each species. To date, 13 functional TLRs have been identified in mammals, 10 known TLRs have been identified in humans (TLR1-TLR10), and 12 TLRs have been identified in mice (TLR1-TLR9, TLR11-TLR13) [24]. TLRs are mainly distributed on the cell surface or in intracellular vesicles such as endosomes, the endoplasmic reticulum (ER), lysosomes. TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10 are expressed on the cells surface and are mainly recognize microbial membrane components. TLR3, TLR7, TLR8, TLR9, TLR11, TLR12, and TLR13 are expressed in intracellular vesicles and primarily recognize microbial nucleic acids and profilins.

TLRs are type I transmembrane molecules consisting of a leucine repeat structural domain in the extracellular region that mediates microbial recognition, a transmembrane region, and a structural domain in the intracellular region that is homologous to the IL-1 receptor (Toll and interleukin 1 receptor, TIR) and is involved in downstream signaling

[16]. TLRs signaling involve the myeloid differentiation factor (MyD) 88-dependent pathway and the MyD88-independent signaling pathway.

In the Myd88-dependent pathway, upon binding to their corresponding ligands, all members of the TLRs with the exception of TLR3 transduce signals through MyD88 to induce a cascade reaction that results in the activation of NF-κB and leads to the production of a wide range of pro-inflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) [15]. MyD88 belongs to a family of junction molecules containing cytoplasmic TIR structural domains [24,25]. Upon ligand stimulation, it interacts with interleukin 1 receptor-associated kinase (IRAK) through the death domain (DD) at the N-terminal end of MyD88 to excute signals transduction. Stimulated IRAK4 activates IRAK1 autophosphorylation, and it further binds to the tumor necrosis factor receptor-associated factor (TRAF) structural domain of TRAF6 upon activation. The IRAK1/TRAF6 complex detaches from the receptor complexes and binds to transforming growth factor beta-activated kinase 1 (TAK1) and TAK1-binding proteins (TAB1, TAB2 and TAB3). Then, TAK1 activates two downstream pathways involving the inhibitor of nuclear factor kappa-B kinase (IKK) complex and the mitogen-activated protein kinase (MAPK) family. In turn, TAK1 activates the IKK complex comprised of the catalytic subunits IKKα, IKKβ, and IKKγ. The IKK complex phosphorylates the NF-kappaB (NF-κB) inhibitory protein IkappaBalpha, and these results in the release of free NF-κB (p50/p65) that promotes translocation of p65 to the nucleus and initiates the transcription of pro-inflammatory genes. TAK1 also leads to the activation of MAP kinases ((extracellular signal-regulated kinase, c-Jun N-terminal kinase (JNK), and p38). Members of the MAPK family phosphorylate and activate the transcription factor activator protein-1 (AP-1) that contributes to inflammatory responses (Fig. 1).

In the MyD88-independent signaling pathway, TLR3, TLR4 and TLR5 that use Toll/IL-1R domain-containing adaptor-inducing IFN-beta (TRIF) as an activator to mediate downstream signals, and this is also known as the TRIF-dependent pathway [24,25]. This pathway is initiated by TRIF-related adapter molecule (TRAM) and TRIF that are important for the recruitment of TNF receptor-associated factor 3 (TRAF3). Once stimulated, TRAF3 recruits IKK-related kinases, and the activation of the TRAF family member-associated NF-κB-binding kinase (TBK1) and IKKi results in interferon regulatory factor 3 (IRF3) activation, dimerization, and translocation to the nucleus to in turn activates interferon (IFN)-induced gene expression and cause the release of inflammatory mediators. TRIF also can directly bind to TRAF6 via its TRAF6-binding motifs. Then TRAF6 activates TAK1 in a manner similar to that in the MyD88-dependent pathway, ultimately leading to NF-κB activation and the induction of inflammatory cytokines (Fig. 1).

Accumulating evidence has demonstrated an association between TLRs and MASLD progression. Human models of MASLD have demonstrated increased expression of several TLRs. There is ample evidence for the role of TLR4, TLR2, TLR1 and TLR9 in the pathogenesis of MASLD, whereas evidence for the roles of other TLRs, including TLR3, TLR5, and TLR7, is limited.

### 3.1. TLR4 and MASLD

TLR4 was the first discovered and described TLRs receptors, and it is located in different cell types in the liver, including hepatocytes, Kuffer cells, and stellate cells. The TLR4 signaling pathway is closely related to the development of MASLD and is involved in hepatic steatosis, hepatitis, and fibrosis. Studies have revealed that the TLR4-TRIF pathway probably is involved in the occurrence of hepatic steatosis [26] and that the TLR4-MyD88 pathway is more inclined towards at the progression of MASH and fibrosis [17]. The expression of TLR4 in different hepatocytes has different effects on MASLD.

#### 3.1.1. TLR4-associated ligands in MASLD

The endotoxin LPS is the classical ligand for TLR4, and it is translocated into systemic circulation as a consequence of increased gut permeability in obesity. TLR4 can interact with myeloid differentiation factor 2 (MD2) [27] and recognize LPS to activate MyD88-dependent

**Table 1**
The role of PRRs on MASLD and their related inhibitors or activator.

| categorisation | | Hepatic cells | ligand | relevance | Inhibitor or activator |
|---|---|---|---|---|---|
| TLRs | TLR4 | Hepatocytes [43,45]<br>Kupffer cells [243]<br>HSCs [244] | LPS [35]<br>FFAs [36] | promote | JKB-121 [58]TLR4-IN-C34 [61]TAK-242 [60] |
| | TLR2 | Kupffer cells [78]<br>HSCs [74] | lipoteichoic acid [72] | promote | TLR2 monoclonal antibody [64]<br>EPS [79] |
| | TLR9 | Hepatocytes [83,245]<br>HSCs [246] | DNA [82]<br>mtDNA [83,245] | promote | IRS [93]<br>IRS954 [84]<br>CpG ODN [91] |
| | TLR1 | Kupffer cells [98] | bacterial triacylated lipopeptides and lipoproteins [94] | promote | / |
| | TLR3 | Kupffer cells [101] | dsRNA [99] | promote | / |
| | TLR5 | Liver sinusoidal endothelial cells (LSECs) [105]<br>Hepatocytes [106] | Bacterial flagellin [106] | promote<br>inhibit | /<br>/ |
| | TLR7 | Kupffer cells [112]<br>HSCs [247] | ssRNA and<br>bacterial DNA [110] | inhibit<br>promote | Imiquimod [111]<br>IRS661 [112] |
| CLRs | Dectin-1 | Kupffer cells [119] | β-Glucans [117]<br>PA [119] | promote | Short-chain β-GlucansLaminarin [119] |
| | LOX-1 | HSCs [128] | FFAs [128] | promote | N-3PUFAS [125] |
| NLRs | NOD1 | Hepatocytes [139] | PGN [135] | promote | / |
| | NOD2 | Hepatocytes [136,137] | PGN [135] | inhibit | / |
| | NLRP3 | Kupffer cells [155]<br>HSCs [248] | ATP [146]LPS [147]<br>FFAs [158] | promote | MCC950 [166]CY-09 [168]Tranilast [170]<br>OLT-1177 [172] |
| | NLRP6 | Hepatocytes [185] | LPS [183] | inhibit | / |
| | NLRP12 | Hepatocytes [189] | LPS [186] | inhibit | / |
| RLRs | RIG-I | Hepatocytes [195] | RNA [193] | inhibit | / |
| | MDA5 | Hepatocytes [199] | dsRNA viruses [197] | inhibit<br>promote | /<br>/ |
| DNAreceptor | STING | Kupffer cells [213]<br>HSCs [249] | mtDNA [205] | promote | / |
| | AIM2 | Hepatocytes [221] | dsDNA [219] | promote | / |

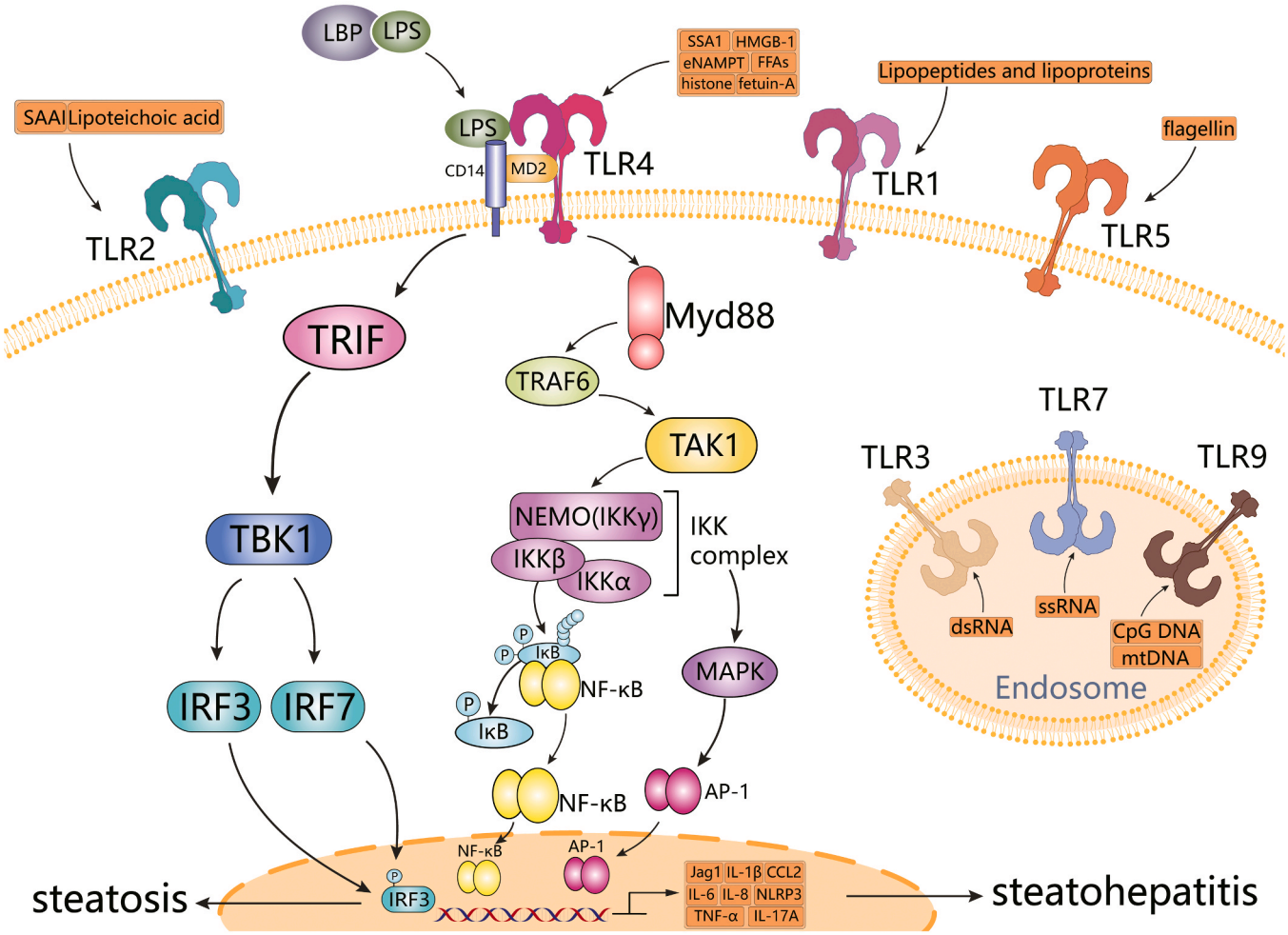


**Fig. 1.** The singaling pathway of Toll-like receptors (TLRs) in the pathogenesis of MASLD. TLRs recognize PAMPs and DAMPs and initiate downstream cascades in TRIF- or MyD88-dependent manner. The activation of IKK, MAPKs and TBK1 kinases trigger dimerization and translocation of NF-κB, AP-1 and IRF3/7 respectively, inducing the expression of cytokines, chemokines, type I interferons, and other pro-apoptotic genes. The secretion of these active factors may contribute to lipid accumulation, inflammation and hepatocyte apoptosis.

NF-κB and MAPK pathways to induce pro-inflammatory cytokine production [27,28]. LPS can not only exacerbate lipid metabolism-associated inflammatory injuries in hepatocytes by increasing macrophage infiltration in the liver, but it can also upregulate the expression of TLR4 on the surface of infiltrated macrophages, Kuffer cells, and stellate cells. This can lead to an increase in the release of inflammatory and chemotactic factors, thus promoting the MASLD process. If excessive signaling occurs through TLR4, it will induce systemic inflammation and cytokine storms [29]. Serum LPS levels are correlated with TLR4-positive macrophages and platelets and are higher in MASH than they are in simple steatosis or controls [30]. The LPS/TLR4/MD2 signaling pathway plays a key role in the pathogenesis of MASLD by inducing inflammation, mediating oxidative stress and participating in the repair of IR and hepatic inflammatory injury and fibrosis [31,32]. Lipopolysaccharide-binding protein (LBP), an acute-phase protein present in blood at high concentrations, is derived from the liver [33]. Studies have demonstrated that high concentrations of LBP attenuate LPS-induced inflammation by forming LBP-LPS complexes that play a protective role in preventing hepatic inflammation, oxidative stress, and fibrosis [34].

In addition to LPS, metabolism-associated molecular pattern (MAMP) [35] and DAMP stimulators have been demonstrated to activate TLR4 signaling, including free fatty acids (FFAs), HMGB1, Alfa 2-Heremans-Schmid (fetuin-A), serum amyloid A1 (SAA1), extracellular nicotinamide phosphoribosyl transferase (eNAMPT), and histones. Elevated levels of circulating FFAs are a hallmark of obesity and overnutrition and in the context of metabolic disorders and overload, a dramatic increase of FFA levels is observed that significantly exceeds physiological concentrations and reaches pathological levels. Saturated fatty acids activate the TLR4 inflammatory pathway in hepatocytes to promote IR, ultimately resulting in elevated blood glucose levels and hepatic steatosis [36].

HMGB1, a highly conserved ubiquitous protein, is a DAMP molecule that can trigger TLR4 receptors generating pro-inflammatory cytokines release. HMGB1 mediates the activation of TLR4 signaling in hepatocytes during the early stages of MASLD in mice [37]. Moreover, HMGB1 released from hepatocytes in response to FFA infusion is a key molecule for TLR4 activation and cytokines expression [38]. Furthermore, there is a close link between JNK1-dependent HMGB1 secretion from lipotoxic hepatocytes and paracrine cytolytic effects on neighboring cholesterol-loaded hepatocytes via TLR4 [38]. Treatment with neutralizing antibodies against HMGB1 protects against FFA-induced TNF-α and IL-6 production [39]. The results indicated that lipid nanoparticles (mLNP-siHMGB1) could target macrophages through mannose receptors, effectively silence the HMGB1 gene, reduce the release of HMGB1 protein in the liver, regulate liver macrophages to induce an anti-inflammatory M2 phenotype, reduce hepatic lobular inflammation and bullous steatosis in the liver, and restore liver function to normal levels in a MASH mouse model [38,40].

Fetuin-A is a glycoprotein secreted by both the liver and adipose

tissues [41]. Modulation of fetuin-A is associated with several pathophysiological variables that cause liver problems, including insulin receptor signaling deficiencies, adipocyte dysfunction, hepatic inflammation, fibrosis, triacylglycerol production, macrophage invasion, and TLR4 activation [42]. SAA1, an acute-phase response protein, can trigger hepatic steatosis and intrahepatic inflammatory response by forming a SAA1/TLR4/NF-κB/SAA1 feed-forward regulatory circuit and this, in turn, leads to MASLD progression in obesity-induced hepatic inflammation [43]. ENAMPT, a novel DAMP and TLR4 ligand, induces the activation of the eNAMPT/TLR4 inflammatory pathway that is a key contributor to MASLD development and progression to hepatic fibrosis [44]. Extracellular histones are ligands of TLR4 and can potentially enhance fibrogenesis via the TLR4-MyD88 signaling pathway [45]. Fibrinogen-like protein 2 aggravates MASH by interacting with TLR4 to elicit inflammation in macrophages and inducing hepatic lipid metabolism disorders [46].

#### 3.1.2. Clinical, animal, and cellular models

Clinical studies have reported that TLR4 expression is up-regulated in a large cohort of MASH patients compared to that in patients with MASLD, and this occurs within the setting of increased LPS and lipid acids levels [28]. TLR4 mRNA levels are significantly higher in patients with MASH than they are in those with MASLD [28]. Moreover, serum TLR4 levels were elevated in patients with MASH compared to those in healthy controls [47]. Hepatic TLR4 expression is associated with portal inflammation and fibrosis in MASLD [48]. These results indicated that TLR4 levels were correlated with the progression of MASLD, particularly in the context of liver fibrosis. Clinical studies examining TLR4 gene polymorphisms in patients with MASLD in comparison to healthy controls reveal that the TLR4 codon 299 heterozygous gene mutation (Asp299Gly) in humans may play a preventive role against the genesis of MASLD [49].

TLR4 plays a key role in lipid accumulation and steatosis. TLR4 deficiency increased fatty acid oxidation, and stimulated β-oxidation in mouse livers, and knockdown of TLR4 attenuated hepatic steatosiss [50]. Moreover, activation of the TLR4 signaling pathway is also essential for the development of liver fibrosis. When fed a high-fat diet (HFD), TLR4 knockout mice exhibited a significantly reduced hepatic inflammatory response in the livers [51]. HFD promotes TLR4-mediated activation of downstream MAPK and NF-κB signaling pathways. Inflammatory genes (IL-6, IL-1β, TNF, C-C motif ligand 2 (CCL2), intercellular adhesion molecule 1, and vascular cell adhesion molecule 1) regulated by the TLR4 pathway were elevated by HFD that in turn exacerbated hepatic inflammation and promoted hepatic fibrosis. The lysosomal degradation of TLR4 by Tmbim1 protects against MASLD in mice and monkeys [52]. The latest research shows that miR-204–3p expression decreased in livers and macrophages in mice and patients with fatty liver, and miR-204–3p-overexpressing macrophages inhibited TLR4/JNK signaling and pro-inflammatory cytokine release, thereby limiting fat deposition and inflammation in hepatocytes and fibrogenic activation in HSCs [53].

The expression of TLR4 in different hepatocytes has different effects on MASLD. Hepatocyte TLR4 triggers inter-hepatocyte Jagged1/Notch signaling to promote MASH-induced fibrosis [54]. Lack of fibroblast growth factor 21 (FGF21) promotes MASH-HCC transition via hepatocyte-TLR4-IL-17A signaling. The negative feedback loop on the hepatocyte-TLR4-IL-17A axis could act as a potential anti-carcinogenetic mechanism by which FGF21 prevents MASH-HCC transition [55]. Furthermore, TLR4-positive macrophages were significantly increased in MASH compared to those in simple fatty liver [30]. A role of TLR4 in mediating the progression of simple steatosis to MASH by inducing reactive oxygen species (ROS) -dependent activation of X-box binding protein 1 in Kupffer cells has also been reported [56]. Pro-inflammatory hepatic infiltrating CD11b+F4/80 macrophages generate ROS through NADPH oxidase 2 via endocytosis of the monomeric TLR4-MD2 complex [57].

#### 3.1.3. Therapeutic inhibitor for TLR4 signaling-associated MASLD

Inhibition of the TLR4 signaling can be effective for the treatment of MASLD. A class of small molecule inhibitors (JKB-121, TAK-242, and TLR4-IN-C34) has been shown demonstrated to be associated with a reduction in the hepatic expression levels of TLR4 and NF-κB and can attenuate the development of MASLD.

The TLR4 antagonist JKB-121 is a long-acting small molecule that acts as a potent, weak antagonist of TLR4 [58]. It is a non-selective opioid antagonist that prevents lipopolysaccharid (LPS)-induced inflammatory liver injury in a methionine/choline-deficient diet (MCD)-fed rat model of MASLD. *In vitro*, JKB-121 neutralizes or reduces the release of LPS-induced inflammatory cytokines, inactivates hepatic stellate cells, inhibits hepatic stellate cell proliferation and collagen expression, and provides an effective treatment for the prevention of inflammatory liver injury and fibrosis in patients with MASH. A Phase 2 RDBPCT clinical trial of JKB-121 for MASH is currently ongoing (NCT02442687).

TAK-242 (Resatorvid) is also a small molecule antagonist of TLR4 that selectively disrupts TLR4 signaling, thus leading to the inability of Toll interleukin 1 receptor domain-containing articulating protein and TRAM to be recruited by binding to the intracellular TIR domain, and this in turn leads to a reduction in the secretion of the cytokines TNF-α and IL-6 and inhibits liver fibrosis in mice [59]. Moreover, TAK-242 treatment inhibits TLR4 signaling, thus preventing the progression of MASH to HCC. TAK-242 improves the response of monocytes and hepatocytes to LPS *in vitro* and can be used to treat LPS-induced acute liver injury [60].

Additionally, TLR4-IN-C34 acts as a TLR4-selective inhibitor by binding to its co-receptor MD-2, and it also inhibits the activation of NF-κB as well as the nuclear translocation of NF-κB, thus modulating the TLR4/MyD88/NF-κB signaling pathway to inhibit inflammation and progression [61].

TLR4 is also closely involved in maintaining the gut microbiota composition. Targeting the gut microbiota is a novel therapeutic approach for the treatment of MASH. It has been observed that modulating the gut flora using *Lactobacillus reuteri* as a probiotic supplement for gram-positive bacteria in combination with MTZ (an antibiotic) can be effective for the treatment of MASH. This correlates with autophagy and the LPS/TLR4 signaling pathway than inhibits lipid accumulation in the liver [62].

In summary, has become an important target for the treatment of MASLD. A variety of TLR4 inhibitors developed so far have been demonstrated to exert certain effects in animal models of MASLD. However, a number of these have already achieved good efficacy they have not yet passed clinical trials, and this may be related to individual differences in the trials [63]. Due to the complex structure of the drugs and the diversity of their underlying mechanisms, the activity of these drugs on TLR4 deserves more in-depth study.

### 3.2. TLR2 and MASLD

TLR2 is a transmembrane receptor with a relatively broad ligand specificity that recognizes gram-positive bacterial components and is expressed on hepatocytes, Kupffer cells, biliary epithelial cells, and stellate cells in the liver. The TLR2/MyD88 signaling pathway is primarily involved in MASH development [64].

#### 3.2.1. Clinical, animal, and cellular Models

One clinical study demonstrated that serum TLR2 levels were not significantly different between healthy controls and MASH patients [47] and that hepatic TLR2 expression at the mRNA levels was elevated in MASLD and MASH patients [65]. Moreover, in the liver of MASH patients, TLR2 is positively correlated with transforming growth factor beta1 (TGF-β1) expression [64] that contributes to the hepatic inflammation in MASH through the Smad3/TLR2 signaling pathway. Circulating IL-8 levels correlate with liver fibrosis in patients with MASLD

[66]. Lipid accumulation in hepatocytes induced IL-8 production, and there is a positive relationship between IL-8 circulating levels and TLR2 hepatic expression in women with morbid obesity and MASH [67]. The latest research indicated that plasminogen activator inhibitor-1 (PAI-1) is associated with MASLD by lipid accumulation in the liver. Correlation analysis confirmed that PAI-1 levels were positively correlated with the TLR2-activating ability of serum from NAFLD patients and healthy subjects [68]. TLR2 is the biomarker closely associated with MASH development.

Although TLR2 is upregulated in the livers of various animal models of MASLD [69,70], the role of TLR2 and its molecular mechanisms are controversial according to different mouse studies. Some studies have reported that TLR2-mediated signaling exerts protective effects against liver injury. The MCD diet-induced liver injury and MASH were more severe after LPS challenge in TLR2-deficient mice [71]. Dietary saturated fat plays a protective role against MCDD-induced steatohepatitis, whereas TLR2 deficiency exacerbates MASH. *A.muciniphila* prevented MASH by modulating TLR2-activated γδT17 cells and further macrophage polarization, thus facilitating clinical therapeutic applications [72]. IFN-γ promotes TLR2 transcription and expression of its target genes by STAT1β. This leads to a vicious cycle of hepatic inflammation in MASH and provides new potential targets for the treatment of MASH. The latest research found that microplastics (MPs) disrupted gut microbiota homeostasis and activated TLR2/NF-κB/NLRP3 pathway in the liver, thereby promoting liver injury [73].

In contrast, the majority studies have indicated that TLR2 signaling is involved in the occurrence and development of MASH. TLR2 and palmitic acid cooperatively contribute to the development of MASH through inflammasome activation in mice [74]. In choline-deficient L-amino-acid (CDAA)-defined diet-induced MASLD, TLR2 deficiency suppressed MASH progression [74]. Down-regulation of miR-144 elicits pro-inflammatory cytokine production by targeting TLR2 in MASH in HFD-induced metabolic syndrome E3 rats [75]. TGF-β1 contributes to hepatic inflammation in animal models with MASH through Smad3/TLR2 signaling pathway [76]. Additionally, there is a Smad3 binding site in the TLR2 promoter region, and TGF-β1 can participate in MASH through the Smad3/TLR2 signaling pathway [76].

TLR2 is predominantly localized in hepatic macrophages and hepatocytes. Previous reports have confirmed that TLR2 and PA synergistically activate inflammatory vesicles in Kupffer cells during MASH development [74]. Hepatocyte-generated SAA1 promotes intrahepatic platelet aggregation and aggravates liver inflammation in MASLD [77]. TLR2 inhibition ameliorates the effect of LPS on lipid accumulation and lipotoxicity in hepatic cells. TLR2 siRNA attenuated the LPS-induced amplification of lipid accumulation in a cell model by modulating the insulin receptor substract 1/phosphoinositide 3-kinase /protein kinase B signaling pathway [78].

#### 3.2.2. Therapeutic inhibitor for TLR2 signaling-associated MASLD

A TLR2 monoclonal antibody attenuated hepatic steatosis, fibrosis, and the inflammatory response in HFD metabolically disordered rats and inhibited the activation of MAPK and NF-κB pathways in an HFD-induced dyslipidemia rat model [64]. Hepatic macrophage marker (CD68) mRNA levels were also reduced in animals after treatment with the TLR2 monoclonal antibody [64]. This implies that blocking TLR2 using a TLR2 antibody may attenuate the MAPK and NF-κB signaling pathways that triggering metabolic inflammation and metabolic dysregulation in adipose tissue and liver.

Extracellular polysaccharides (EPS) isolated from *Lactobacillus plantarum* L-14 extract can interact with TLR2 to activate the AMP-activated protein kinase (AMPK) signaling pathway, thereby inhibiting adipogenesis and attenuating HFD-induced steatohepatitis. Therefore, EPS could attenuate TLR2 and AMPK-mediated MASLD in HFD-induced obese mice [79].

Normalization of gut microbiota using probiotics or prebiotics is a promising treatment option for MASLD. Additionally, TLR signaling in the liver is activated, and the levels of its downstream molecules such as pro-inflammatory cytokines are increased in MASLD. Certain traditional Chinese medicines exhibiting anti-inflammatory effects related to TLR2 signaling such as *Gynostemma pentaphyllum* (GP) have been used to effectively treat MASLD. *Gynostemma pentaphyllum* polysaccharides ameliorate MASH in mice that is associated with the gut microbiota and the TLR2 pathway [80].

Summarily, TLR2 is primarily involved in the occurrence and development of MASH. However, the results regarding TLR2 are controversial. Therefore, a better understanding of the mechanism of TLR2 signaling in the context of HFD-induced liver injury could provide new ideas for the development of novel therapeutic drugs.

### 3.3. TLR9 and MASLD

TLR9 is present only on endosomal membranes, and rarely on cell membranes [81]. TLR9 primarily binds to cytosolic CpG motifs in bacterial DNA and triggers signaling cascades that lead to pro-inflammatory cytokine responses [82]. TLR9 can also be activated by endogenous circulating mitochondrial DNA (mtDNA). Chronically elevated circulating levels of mtDNA caused by overnutritional stress are observed in obesity, MASLD, and MASH. Plasma from mice and patients with MASH contain mtDNA from hepatocytes that can also act as a ligand for TLR9, ultimately leading to the development of steatohepatitis, fibrosis, and insulin resistance [83,84]. Most plasma mtDNA is contained in MPs of hepatocyte origin, and the removal of these MPs result in a significant decrease in TLR9 activation capacity.

#### 3.3.1. Clinical, animal, and cellular Models

Clinical studies have revealed that TLR9 expression is significantly upregulated in the livers of patients with MASH, but not in the livers of patients with mild steatosis [85,86]. Co-stimulation of T cells from patients with simple steatosis by TLR9 ligands induced CD8+T cells to produce IFN-γ [85]. The positive associations between TLR9 and anthropometric, clinical, and histological features of MASLD and the crucial role of IFN-γ in MASLD suggest that limited TLR9 expression and production of IFN-γ play a protective role in patients with simple steatosis [85].

In animal models, deficiency in TLR9 under hepatic fibrosis is accompanied by elevated ALT levels, whereas TLR9 KO mice do not develop severe MASH. MyD88 acts as a downstream signaling adaptor molecule for TLR9, and MyD88 and TLR9 deficiency protects against CDAA diet-induced steatosis, hepatic injury, inflammation, and fibrosis [87]. Furthermore, in MCD-induced steatohepatitis, the activated TLR9/MyD88 signaling pathway augments inflammasome up-regulation and dietary induced-steatohepatitis [88]. The latest research findings extracellular histones initiate hepatocellular pyroptosis and liver injury through the TLR9-NLRP3 pathway, thereby exacerbating heat-stroke-induced liver injury [89]. These data suggest that the activation of the TLR9 pathway provides a link between key metabolic and inflammatory phenotypes in MASH.

#### 3.3.2. Therapeutic inhibitor for TLR9 signaling-associated MASLD

Certain therapeutic inhibitor molecules associated with TLR9 signaling are the current therapeutic targets for MASH [90]. The use of the TLR7/9 antagonist IRS954 prevented MASH and elevated ALT and cytokine transcript levels (pro-IL-1β, IL-6, and TNF-α) [84]. Additionally, as an adjuvant, CpG ODN can stimulate B-cell viability and enhance the antibody response to vaccines by alleviating the negative regulation of TLR9 on the surface of B cells, thus suggesting that a certain degree of precision therapy is possible in complex diseases [91].

In summary, TLR9 leads to the development of MASLD through mtDNA recognition [92] that has become an current therapeutic target for MASLD treatment. Some TLR9 antagonist analogs, such as IRS [93] and IRS954 [84], are undergoing clinical trials in other disease, but are not currently validated for use in MASLD, which requires further clinical

studies.

### 3.4. TLR1 and MASLD

TLR1 is widely distributed, highly expressed, and recognizes bacterial triacylated lipopeptides and lipoproteins [94] that are closely related to the gut microbiota [95]. In MASLD, gut bacterial diversity is reduced, and dysregulation of the gut microbiota can interfere with hepatic carbohydrate and lipid metabolism, ultimately affecting the balance between pro- and anti-inflammatory effectors in the liver and thus contributing to MASLD and its progression to MASH [96,97]. In the progression of MASLD to MASH, TLR1 expression was significantly positively correlated with the abundance of the harmful bacterium *Holdemanella spp.* and negatively correlated with the abundance of the beneficial bacteria *Gemmiger spp.* and *Ruminococcusspp* [95]. Although there are significant differences in gut flora composition and permeability between MASLD patients and healthy subjects, only TLR1 expression differed in the peripheral blood mononuclear cells (PBMCs) of MASLD mice and could be induced by LPS and lipoteichoic acid (LTA) [95].

Mice deficiencies in TLR1 were significantly protected against the development of diet-induced MASLD. Another study indicated that TLR1 expression was upregulated in the livers of HFD mice compared to levels in normal diet mice and that was downregulated by hepatoprotective orphogenetic protein (BMP)-9 treatment. BMP-9 may alter the number or composition of hepatic macrophages and ultimately reduce liver inflammation by affecting TLR1 expression [98].

In brief, TLR1 is involved in the development and progression of MASLD through HFD and alterations in the composition of the intestinal flora. However, the information about TLR1 is still less that need further to explore.

### 3.5. TLR3 and MASLD

TLR3 is present in intracellular vesicles, such as nuclear endosomes and lysosomes, and it recognizes dsRNA and polyinosinic-polycytidylic acid (poly I:C) as well as viral genomic RNAs [99]. TLR3 is also located on the surface of epithelial and Kupffer cells in the liver. Several studies have observed that the activation of TLR3 leads to the production of type I IFNs and inflammatory cytokines, ultimately resulting in an antiviral immune response.

A clinical study demonstrated that TLR3 was significantly induced in the livers of patients with MASH compared to that in normal subjects [100]. ~~Additionally~~Moreover, TLR3 expression was upregulated in the livers of overweight and obese mice. An animal study indicated that TLR3 deficiency play a protective role in the development of HFD diet-induced steatosis and hepatic inflammation in mice [101]. In another study, TLR3-deficient mice also exhibited less steatosis after HFD [102]. Moreover, heat shock protein 60 restricts the release of mitochondrial dsRNA to repress the TLR3 pathway, suppress hepatic inflammation and ameliorate MASLD in mice [103]. As far as the present study shows that loss of TLR3 protect hepatic steatosis that suggests antagonizing TLR3 may be a beneficial therapeutic approach for the treatment of fatty liver.

### 3.6. TLR5 and MASLD

TLR5 recognizes flagellin proteins in gram-negative bacteria. TLR5 is mainly expressed in hepatocytes and liver sinusoidal endothelial cells (LSECs) that are involved in the innate immune response during the pathogenesis of MASLD [104–106]. A clinical study has demonstrated that the TLR5 rs5744174 polymorphism is linked to the occurrence of HCC in cirrhosis caused by steatohepatitiss [107]. Additionally, a genetic variant of TLR5 is associated with chemokine levels in steatohepatitis, and TLR5 is associated with liver disease progression in animal models [108,109].

However, the functions of TLR5 in hepatocytes and LSECs remain controversial. One study indicated that mice lacking TLR5 exhibit microbial dysbiosis and a predisposition to HFD-induced hepatic steatosis. Hepatic TLR5 protects the liver from infection by circulating intestinal bacteria and plays a key role in HFD-induced liver diseases [106]. However, a recent study indicated that *E.coli* promoted the development of MASLD and endothelial-mesenchymal transition in LSECs through TLR5/NF-κB dependent activation mediated by flagellin. Therapeutic interventions targeting *E.coli* and/or flagellin may be promising for the treatment of MASLD [105]. Therefore, the regulation of lipid metabolism in the liver by TLR5 remains controversial, and further TLR5-related mechanistic studies are required in the context of MASLD.

### 3.7. TLR7 and MASLD

TLR7 recognizes viral and bacterial RNAs [110]. A study has revealed that TLR7 affects lipid accumulation in hepatocytes by regulating autophagy and lipid peroxidation [111]. MASLD was severely reduced in TLR7 knockout mice fed an unsaturated fatty acids diet. TLR7 can prevent the progression of MASLD-induced autophagy by inducing the release of insulin-like growth factor 1 in hepatocytes through MyD88 signaling, and this in turn inhibits the development of MASLD [111]. The progression of MASLD is massively and continuously accelerated by the lipid peroxidation products malondialdehyde (MDA) and 4-hydroxynonenal via the blockade of TLR7. The TLR7 agonist imiquimod inhibited intrahepatic lipid accumulation. Imiquimod was developed by 3 M Pharmaceuticals and is one of the most successful TLR7-targeting drugs, and it acts as a small-molecule agonist by activating the TLR7-dependent MyD88 signaling pathway [111].

However, another study demonstrated that TLR7 signaling promotes MASH by inhibiting regulatory T cells in mice [112]. Mechanistically, TLR7 signaling mediates the production of TNF-α and type I IFN in Kuffer cells and dendritic cells, respectively, and this induces hepatocyte death and inhibits Treg cell activity, ultimately leading to steatohepatitis. Treatment with the TLR7antagonist IRS661 is effective for improving MASH in vivo [112].

TLR7 probably plays different roles in the process of steatosis and MASH. Although TLR7 agonists and antagonists have been observed to be associated with MASLD treatment, they have not been clinically applied. Therefore, more trials are required for the clinical validation of drugs on TLR7.

## 4. CLRs

CLRs are an important class of PRRs that recognize self and non-self ligands in humans and protect against invading pathogens by modulating immune recognition and response. CLRs were originally defined as a class of $Ca2^{+}$-dependent sugar-binding transmembrane molecules that are expressed predominantly on myeloid cells and share the common feature of a protein structure with a folding domain capable of binding to C-type glycan recognition domains that can bind sugars. With the discovery of more C-type lectins, the co-ligands were not only limited to sugars but also to proteins and lipids. Thus the C-type glycan recognition domain was expanded to a C-type lectin-like domain [113].

Seventeen classes of CLRs that perform a variety of functions have been identified in vertebrates. CLRs primarily recognize fungal and bacterial PAMPs and induce the downstream expression of innate immune response genes. CLRs induce downstream gene expression in two manners. Dectin-1 is the only CLR that recognizes PAMP and directly induces downstream signaling via hemimmunoreceptor tyrosine-based activation (hemITAM). Other CLRs recognize pathogenic microorganisms and transmit downstream signals via basic amino acid residues in their transmembrane regions. They non-covalently interact with immunoreceptor tyrosine-based activation motif (ITAM)-containing junction proteins to activate splenic tyrosine kinase (Syk) that indirectly induces downstream gene expression [114]. **(**Fig. 2**)**

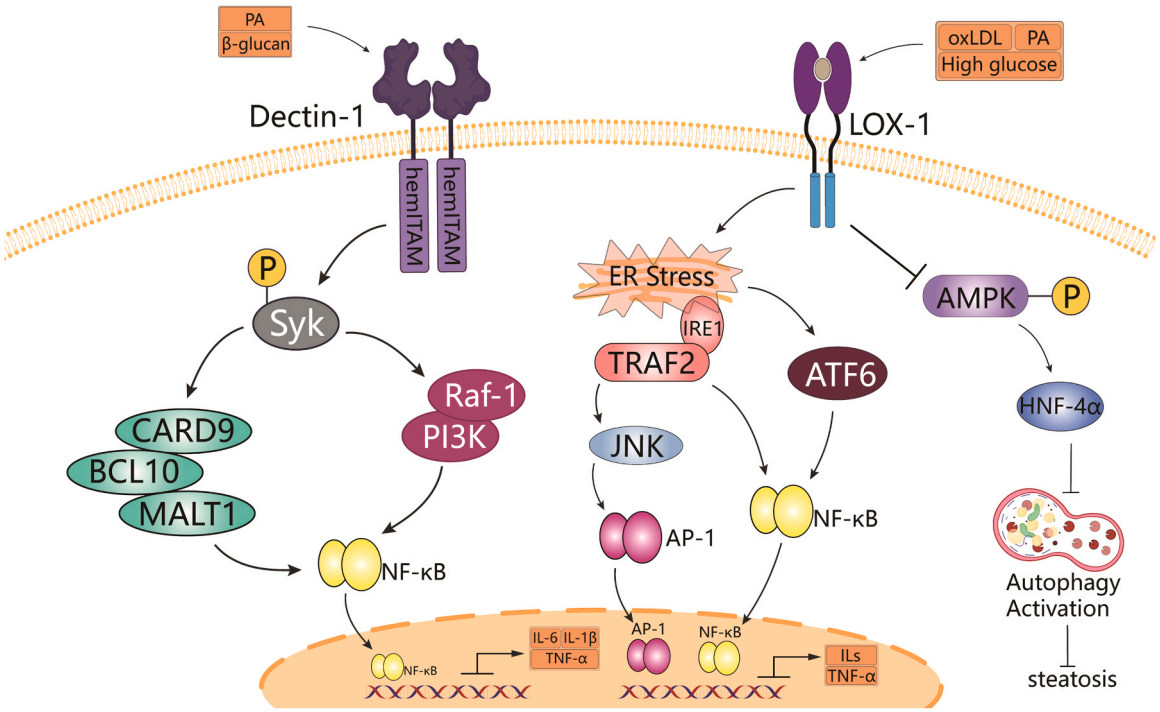


**Fig. 2.** The role of Dectin-1 and LOX-1 in the pathogenesis of MASLD. Dectin-1 can recognize β-glucans and palmitic acid (PA), then mediate pro-inflammatory intracellular signals, including Syk and NF-κB to induce cytokines and chemokines. LOX-1 can recognize fatty acids, oxLDL and High glucose, which cause the activation of ER stress, increase theexpression of ATF6 and IRE1, thereby activating the JNK and NF-κB signaling pathway. In addition, LOX-1 can inhibit the autophagic activity via the AMPK/HNF4α pathway in high glucose-induced HLSECs. Activation of Dectin-1 and LOX-1 signaling axis could promote lipid accumulation, inflammation of liver disease.

### *4.1. Dectin-1 and MASLD*

Dectin-1 is one of the most extensively studied CLRs. Dectin-1 is mainly expressed in activated myeloid cells and is essential for regulating immune homeostasis. It mediates the recognition and phagocytosis of fungi and plays an important role in host defense. Human Dectin-1 is encoded by the 28 kDa C-type lectin structural domain family 7 member A [115]. Dectin-1 is selectively spliced to produce eight structurally distinct isoforms from A to C, with isoform A being predominant [116].

Dectin-1 is unique in that its intracellular region contains the hemITAM motif that recognizes β-Glucansin fungal pathogens and then mediates pro-inflammatory intracellular signals, including Syk and NF-κB [117]. Dectin-1, upon activation by β-glucan conjugating enzymes, induces the production of cytokines and chemokines, including TNF-α, chemokine CXC ligand 2 and ILs [118]. Additionally, in primary mouse peritoneal macrophages, Dectin-1 induced intracellular syk signaling in response to palmitoleic acid, and src kinase phosphorylated tyrosine residues of Dectin-1 and created sites for Syk activation via caspase recruitment domain-containing protein (CARD9), metastasis-associated lung adenocarcinoma transcript, and B cell lymphoma/leukemia-10 (Bcl10) to promote downstream signaling to activate NF-κB and inflammatory cytokine production [116] (Fig. 2).

Dectin-1 signaling can cause hepatic inflammation [119]. Dectin-1 expression is significantly elevated in the liver tissues of patients with MASH. It was observed that HFD feeding also increased Dectin-1 levels, and this was associated with macrophage infiltration. It was revealed that high levels of Dectin-1 were harmful to the liver by enhancing macrophage-mediated pro-inflammatory responses in mouse livers. Dectin-1-deficient macrophages are unable to elicit hepatocyte lipid accumulation and hepatic stellate cell activation and that knockout of Dectin-1 or treatment with antagonist durgs such as short-chain β-Glucanslaminarin largely protects the liver from HFD-induced lipid accumulation, fibrosis, and exacerbation of inflammatory responses [119]. Addtionally, treatment with antifungal drugs reduced the severity of liver inflammation and injury [120]. The latest research findings the CCl4-induced hepatitis model showed that Dectin-1 deficiency led to reduced inflammation through decreased inflammatory cell infiltration and lower pro-inflammatory cytokine levels. Moreover, in a NASH model induced by streptozotocin and a high-fat diet, hepatic inflammation and fibrosis were ameliorated in Dectin-1-deficient mice [121]. These results suggest that Dectin-1 may be an important target for the treatment of MASLD

In summary, Dectin-1 is in involved ~~can cause~~ the regulation of hepatic steatosis and hepatic inflammation. As a therapeutic target of MASLD, Dectin-1 antagonist drug β-Glucanslaminarin is effective in animal models. However, this has not been verified in clinical practice, and further clinical studies are urgently required.

### *4.2. LOX-1 and MASLD*

Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1/OLR1/CLEC8A) is a CLR present in endothelial cells, macrophages, platelets, and smooth muscle cells. It has been observed to be upregulated in obese rodent models and humans [122].

The latest research points out molecular mechanisms associated with lipid metabolism, oxidative stress and inflammation might be related to lower expression of LOX-1 in the liver [123]. It has been reported that endoplasmic reticulum (ER) stress plays a crucial role in the development of both steatosis and MASH [124]. LOX-1 is essential for HFD-induced ER stress, and the upregulation of LOX-1 and activation of ER stress promote MASLD development [125]. *In vivo*, HFD enhanced the expression of LOX-1 and induced ER stress, whereas *in vitro*, overexpression of LOX-1 significantly enhanced ER stress in a human normal hepatocyte cell line, ultimately promoting the progression of MASLD. In response to ER stress, inositol-requiring enzyme 1 (IRE1) binds to TRAF2 and activates NF-κB and JNK [126]. JNK acts as a kinase that regulates AP-1 transcription factor and stimulates the expression of

pro-inflammatory mediators that then promote the development of MASLD [127].

LOX-1 is an important target molecule that regulates autophagy in human liver sinusoidal endothelial cells (HLSECs). LOX-1 promotes hepatic lipid accumulation by inhibiting autophagy in HLSECs [128]. Dysfunctional hepatic autophagy in patients with MASLD is associated with overall disease progression [129]. High glucose increased the expression of LOX-1 in HLSECs and attenuated autophagy. Knockdown of LOX-1 could increase autophagy in HLSECs through activation of AMPK and consequently inhibition of the HNF4 signaling pathway [128].

N-3 polyunsaturated fatty acids (PUFAs) have been demonstrated to reduce hepatic lipogenesis and modulate inflammatory responses in mice, and N-3 PUFAs can alleviate HFD-induced MASLD by down-regulating LOX-1 expression and ER stress, thus suggesting that the ratio of N-3 PUFA supplement in the diet may alleviate the development of MASLD [125]. In summary, in both mouse and human livers, LOX-1 probably promotes MASLD development by activating ER stress or attenuating autophagy, which has become a new target for MASLD treatment. Inhibition of the expression of LOX-1 with treatment could ameliorate HFD-induced MASLD [125]. Therefore, the development of LOX-1-associated pharmacological drugs is worth more in-depth.

## 5. NLRs

NLRs are a family of cytoplasmic PRR proteins discovered in recent years that are primarily expressed in the cytoplasm of immune cells, epithelial cells, macrophages, and neutrophils and play a considerable role in host defense. A total of 23 members of the NLRs have been identified in humans, and 34 members have been identified in mice [130]. NLR proteins are characterized by the presence of three homologous structural domains that include the central nucleotide-binding and oligomerization structural domain (NACHT), the C-terminal leucine-rich repeat structural domain (LRR), and the N-terminal effector structural domain [131]. The NACHT domain is important for oligomerization, the LRR structural domain is important for ligand recognition, and the N-terminal effector structural domain allows for recruitment of downstream signaling molecules [132].

NLRs are divided into four subgroups that include NLRA, NLRB, NLRC, and NLR family pyrin domain-containing protein (NLRP) [133]. NLRC and NLRP are key receptors involved in inflammation caused by the disruption of cellular homeostasis during pathogen invasion. The NLRC subgroup comprises NOD1 and NOD2 that promote ER stress by recognizing bacterial peptidoglycans [134]. The NLRP family is comprised of more than 20 species. Some of these, such as NLRP1, NLRP3, NLRP6, NLRP9b, NLRP12, and NLRC4 have been described to form inflammasome complexes. The involvement of NLR in MASLD is widely recognized.

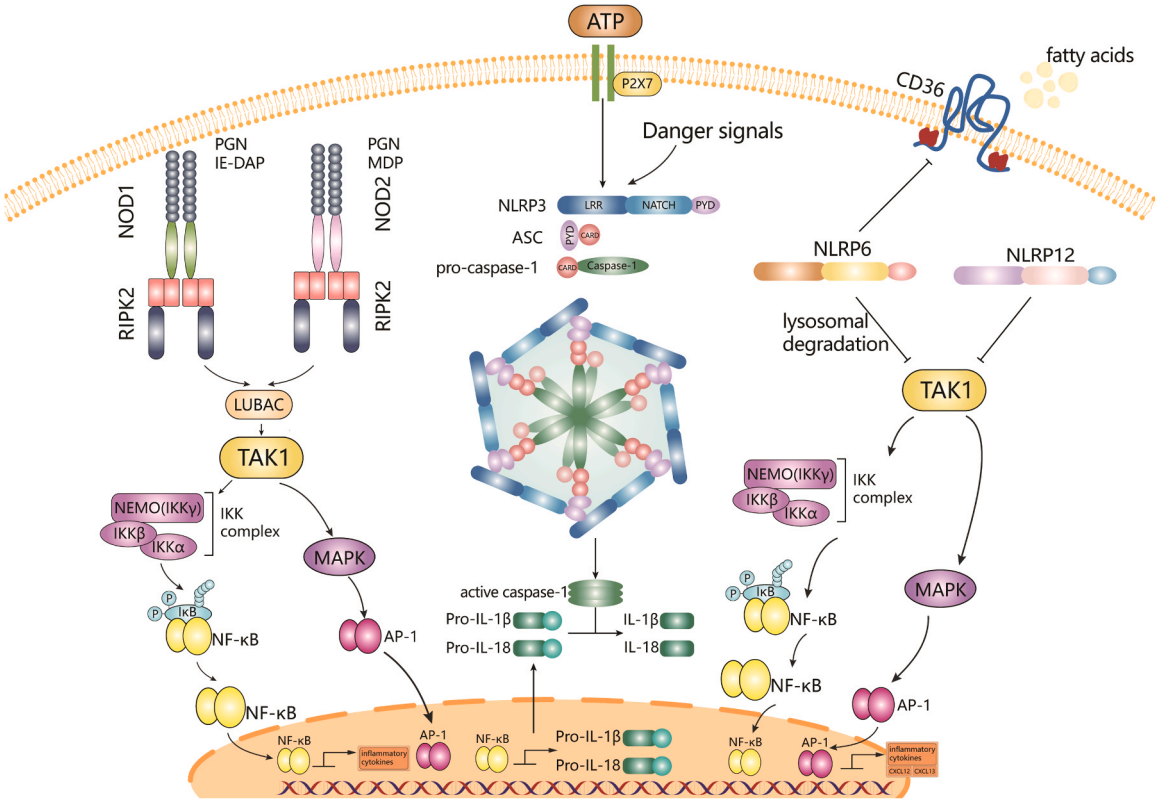


**Fig. 3.** The role of NOD1/2, NLRP3, NLRP6, and NLRP12 in the pathogenesis of MASLD. NOD1 and NOD2 are directly identified in bacterial PGN fragments containing the IE-DAP and intracellular bacterial PGN fragments containing the MDP motif, respectively. Ligand recognition relieves intramolecular autoinhibitory interactions, leading to NOD1/2 oligomerization and recruitment of the downstream serine/threonine kinase RIPK2 through CARD-CARD interactions, resulting in close proximity of RIPK2-IkB kinase (IKK) complexes. RIPK2 then mediates the recruitment and activation of the serine/threonine kinase. TAK1, which is a pre-requisite for activation of the IKK complex and MAPK pathway, IKK and MAPK can boost NF-κB and AP-1 to translocate to the nucleus and influence the expression of downstream target genes. LUBAC stands for linear pUb chain assembly complex. Formation of the NLRP3 inflammasome occurs via oligomerization of NLRP3 monomers to NLRP3 oligomers, which leads to the recruitment of ASC via the PYD domains of NLRP3 and ASC. This in turn leads to the recruitment of pro-caspase-1, which via its CARD domain associates with the CARD domain of ASC. The NLRP3-ASC-pro-caspase-1 complex facilitates the autocatalytic activation of pro-caspase-1, which in turn cleaves pro-IL-1β and pro-IL-18 and the release of IL-1β and IL-18. NLRP6 inhibited CD36-mediated lipid uptake and promoted the degradation of transforming growth factor-β-activated kinase 1 (TAK1)-binding protein 2/3 (TAB2/3) via a lysosomal-dependent pathway, which suppressed the activation of NF-κB and MAPK. NLRP12 inhibited activation of TAK1, thus restrained NF-κB and MAPK signaling pathway.

### 5.1. NOD1/2 and MASLD

The nucleotide-binding oligomerization domain (NOD) proteins NOD1 and NOD2 are members of the intracellular NLRC family that recognize conserved motifs in bacterial PGN and induce pro-inflammatory and antimicrobial responses. NOD1 and NOD2 exhibit similar tripartite architecture, consisting of a C-terminal leucine-rich-repeat (LRR) domain responsible for ligand binding, a central nucleotide-binding domain responsible for ligand-induced oligomerization, and an N-terminal caspase activation and recruitment domain (CARD) responsible for signaling [135]. **(**Fig. 3**)**

Increased NOD1/2expression has been reported in a range of human metabolic diseases, including obesity, diabetes, and MASLD [136,137]. NOD1/2 double-knockout mice are protected from HFD-induced inflammation, lipid accumulation, and peripheral insulin tolerance [138]. The NOD1 ligand resulted in hepatic lipid accumulation and IR, but this phenomenon was not observed in NOD1-deficient mice [139]. However, NOD2 ligands exerted a weak effect on peripheral blood glucose levels. Moreover, NOD2 knockout mice exhibited higher levels of hepatic steatosis and fibrosis [136]. During HFD diet-induced MASLD, NOD2 can inhibit the intestinal ecological dysregulation-caused progression of MASLD, including attenuation of hepatic steatosis and fibrosis [136].

In summary, NOD1 and NOD2 probably play distinct roles in MASLD and the role of NOD1 in hepatic lipid accumulation is unclear [138], whereas NOD2 plays a protective role in the development of metabolic diseases by altering the composition of the intestinal flora. There are no effective drug therapies associated with MASLD for NOD1 and NOD2, and this await further investigation.

### 5.2. NLRP3 and MASLD

NLRP3 has three structural domains that include the amino-terminal pyrin structural domain (PYD), the central NACHT structural domain, and the LRR domain. LRR domains primarily mediate protein-protein interactions, and the LRR of NLRP3 has also been implicated in maintaining stability. The PYD structural domain of NLRP3 interacts with other inflammasome proteins, and these interactions are regulated by phosphorylation [140]. The central NACHT domain possesses ATPase activity that is essential for the self-binding and multimerization of NLRP3, and it may undergo ATP-dependent self-oligomerization, thus resulting in self-PYD interactions that further recruit the adaptor [141] (Fig. 3).

NLRP3 detects exogenous pathogenic microbes ~~invasions~~ and endogenous cellular damage and responds by forming the NLRP3 inflammasome. The NLRP3 inflammasome consists of the sensor protein NLRP3, the adapter protein ASC (CARD-containing apoptosis-associated speck-like protein), and the effector procaspase-1. The NLRP3 inflammasome exhibits a two-step model of initiation and activation. The first step of inflammasome induction is the initiation signals, such as HMGB1 or LPS that leads to the activation and up-regulation of NLRP3, pro-IL-1β, and pro-IL-18 [18]. The second step involves triggering inflammasome formation by specific stimuli, and this is a signal for caspase-1 activation. The adaptor ASC contains two interacting structural domains that include an amino-terminal PYD and a carboxy-terminal CARD. Upon detection of specific stimulus sensor proteins, NLRP3 interacts with ASC through the homotypic PYD-PYD domain to recruit procaspase-1 with the CARD-CARD structural domain [142,143]. Activated caspase-1 further cleaves pro-inflammatory cytokines of the IL-1 family such as IL-1β and IL-18 [144]. Caspase-1 can also induce the expression of gasdermin D that mediates pore formation in the plasma-membrane, osmotic swelling in cells, and pyroptosis induction, ultimately leading to a cascade of pro-inflammatory cytokines release [145].

It has been observed that NLRP3 inflammasome can be triggered by many stimulators such as ATP [146], LPS [147], fatty acids [148], cardiolipin [149], cholesterol crystals, ER stress, oxidized mtDNA [150], perfluorooctanoic acid [151], uric acid [152], secreted protein acidic and rich in cysteine [153] in the liver. The activated NLRP3 inflammasome can lead to the release of inflammatory cytokines, and interaction between inflammatory factors and the pyroptosis-induced hepatic inflammatory fibrosis microenvironment, which promotes the development of MASLD. Particularly, uric acid directly induces hepatocellular fat accumulation and hepatic steatosis via NLRP3 inflammasome. Serum uric acid levels are significantly elevated in patients with MASLD and this can be used to predict the incidence of MASLD in healthy individuals [152].

#### 5.2.1. Clinical, animal, and cellular models

Compared to healthy controls, the mRNA levels of NLRP3 inflammasome components (NLRP3, caspase-1, IL-1β, and IL-18) were significantly upregulated in the PBMCs of MASLD patients. Consistently, plasma levels of mature IL-1β and IL-18 in MASLD patients were significantly higher than they were in controls [154]. Caspase-1 is also present in the serum of patients with MASLD and is closely correlated with the disease severity. Moreover, MASLD patients exhibited increased hepatic mRNA expression of NLRP3, caspase-1, and IL-1β [153]. Addtionally, NLRP3, caspase-1, pro-IL-1β, and pro-IL-18 were significantly higher in the liver samples from MASH patients compared to that in non-MASH groups, and their expression was associated with the degree of fibrosis.

NLRP3 plays a key role in various MASLD/MASH mouse models. NLRP3 knockout mice exhibited blocked development of MASH and attenuated palmitoleic acid-induced inflammatory response in Kupffer cells [155]. In another HFD-induced MASLD mouse model, it was observed that knockout of NLRP3 attenuated hepatic steatosis compared to that in wild-type mice [156]. NLRP3 deficiency ~~protectes~~ protects against infiltration of activated macrophages, liver injury, and diet-induced steatohepatitis and fibrosis [157]. NLRP3 deletion modulates hepatic fibrosis and attenuates age-related hepatic fibrosis. Furthermore, when stimulated with low doses of LPS, these mice exhibited increased susceptibility to inflammation and liver injury [158]. In an MASLD mouse model, NLRP3 deficiency resulted in a more severe pathological profile, ultimately leading to disruption of the gut-liver axis and dysregulation of intestinal ecology [159]. Down-regulation of the NLRP3/NF-κB signaling pathway in mice inhibites MASLD, thereby attenuating the inflammatory response in the mouse liver [160]. Thus, NLRP3 is critical for the MASLD development.

NLRP3 is highly and primarily expressed in Kupffer cells, hepatic stellate cells, and hepatocytes, and its activation aggravates MASLD and pro-inflammatory cytokines IL-1β and IL-18 secretion. Hepatocyte NLRP3 interacts with ~~PKC~~ε protein kinase Cepsilon to drive hepatic IR and steatosiss [161]. Primary mouse and human hepatocytes can undergo pyroptosis upon NLRP3 inflammasome activation, with the subsequent release of NLRP3 inflammasome proteins that amplify and perpetuate inflammasome-driven fibrogenesis [158]. In addition, NLRP3 inflammasome activation by fatty acids in mouse Kupffer cells/macrophages drives the MASH development [162]. The latest research results show that NLRP3 activation in neutrophils induces lethal autoinflammation, liver inflammation, and fibrosis [163]. NLRP3 deficiency in nonimmune Cells also averts obesity-induced Fatty Liver Disease [164].

#### 5.2.2. NLRP3 inhibitor for MASLD treatment

In experimental models, inhibitors and related drugs of the NLRP3 inflammasome have been used to treat MASLD/MASH with positive effects. Several NLRP3 inflammasome inhibitors have been developed, including MCC950 (CP-456, 773 or CRID3), N14, CY-09, tranilast, Bay11–7082, glibenclamide, and JT001. MCC950 significantly blocked the expression of NLRP3 and ameliorated MASH pathology and lipid deposition, and hepatic NLRP3, active caspase-1, pro-IL-1β and pro-IL-18 levels were significantly reduced [165,166]. A series of NLRP3

inflammasome inhibitors based on MCC950 was designed and synthesized, and the representative inhibitor N14 exhibited superior pharmacokinetic properties with good oral bioavailability and was more effective than MCC950 in multiple NLRP3-related animal models of MASH [167]. CY-09 directly binds to NLRP3 and inhibits its ATPase activity, thus inhibiting NLRP3 inflammatory vesicle assembly and subsequent IL-1β production and reducing hepatic steatosis in experimental MASLD mice [168,169]. Tranilast, an analog of a tryptophan metabolite, was initially considered as an anti-allergic agent and is used for the treatment of various inflammatory diseases [170]. Moreover, as a direct NLRP3 inhibitor, tranilast ameliorates MASH in a dietary rat model [171]. Bay11–7082 is a phenyl vinyl sulfone compound that inhibits the NF-κB pathway by blocking IKK-β kinase activity through the alkylation of essential nucleophilic residues. As the prevalence of MASLD is strongly associated with obesity and diabetes, the NLRP3 inhibitor glibenclamide has been used for MASLD treatment. In a clinical trial (NCT00494312), glibenclamide was observed to exert similar effects to those of pioglitazone in patients with type 2 diabetes, with a favorable safety profile for long-term liver use. Other inhibitors such as OLT1177 and NT-0796 specifically inhibited the activation of the NLRP3 inflammasome [172], and they should be tested as potential therapeutic effects against MASLD/MASH. A novel and highly specific NLRP3 inhibitor, JT001, potently and selectively inhibits NLRP3 inflammasome assembly. Orally administered JT001 was effective for reducing hepatic inflammation in three different murine models that included the Nlrp3A350V/CreT model of Muckle-Wells syndrome (MWS), a diet-induced obesity MASH model, and a choline-deficient diet-induced MASH model. Significant reductions in hepatic fibrosis and cell damage have been observed in MWS and choline-deficient models [173].

In summary, the overactivation of the NLRP3 inflammasome can lead to inflammatory diseases. NLRP3 is not only involved in the process of hepatic lipid accumulation but also in the occurrence and development of MASH. Inhibition of activated NLRP3 signaling by stimulants has become an important approach for the treatment of MASLD. Currently, the developed NLRP3 inhibitors have proven to be effective for treating MASLD, and further clinical research is required in the future.

### 5.3. NLRP6 and MASLD

NLRP6 is structurally similar to the more well-studied NLRP3 and consists of a C-terminal LRR, a central NACHT structural domain and an N-terminal PYD structural domain [174]. NLRP6 plays a key role in regulating innate immunity and host defense [175,176]. Similar to other members of the NLRs family, it can also assemble to form an inflammasome with ASC and caspase-1, thus promoting the maturation and secretion of IL-18 and IL-1β and inducing cellular pyroptosis [177,178]. Additionally, NLRP6 inhibited the activities of NF-κB and MAPK [179,180]. NLRP6 has been observed to be highly expressed in the intestine and liver [181].

#### 5.3.1. Clinical, animal, and cellular models

The importance of NLRP6 in the context of liver disease is emerging. One study observed that NLRP6 expression was reduced in human liver biopsies from patients with fibrosis and cirrhosis, thus suggesting a potential role of NLRP6 in human MASLD. The study also demonstrated that NLRP6 can play an anti-fibrotic role by inhibiting cell proliferation, type I collagen and α-smooth muscle actin [182].

Other studies have revealed a correlation between the altered intestinal flora and metabolic diseases in NLRP6 deletion mice. NLRP6 deficiency alters the composition of the gut microbiota through the influx of TLR4 and TLR9 agonists into portal circulation [183]. Microbiota-modulated metabolites shape the intestinal microenvironment by regulating NLRP6 inflammasome signaling [177]. NLRP6-deficient mice exhibited increased hepatic steatosis, inflammatory cell infiltration, and hepatic fibrosis [183]. NLRP6 can maintain intestinal environmental homeostasis and the composition of the intestinal flora that can effectively prevent MASLD from developing into MASH or even reduce the incidence of MASLD [184]. NLRP6 overexpression ameliorated hepatic steatosis and inflammatory responses in ob/ob mice [185]. Moreover, dysbiotic NLRP6-deficient mice displayed exacerbated acetaminophen- and LPS-induced liver injury through regulation of the intestinal microbiota. NLRP6-deficient mice can induce an imbalance in the gut microbiota to cause HCC development by shaping the hepatic inflammatory microenvironment.

Additionally, in primary hepatocytes, saturated fatty acids-induced lipid accumulation decreased the expression of NLRP6, and NLRP6 overexpression significantly attenuated lipid accumulation. Fatty acid uptake enhanced by NLRP6 deficiency in hepatocytes was blocked by treatment with a CD36 inhibitor. NLRP6 promotes the activation of TAK1-binding protein 2/3 (TAB2/3) by TGF-β through lysosome-dependent pathway degradation, thereby inhibiting NF-κB activation [185] (Fig. 3). In cuprocytes, NLRP6 regulates mucus production that prevents the bacterial invasion of the intestine, thereby inhibiting the pathological processes of MASLD and MASH [183].

In summary, NLRP6 can effectively prevent MASLD from developing into MASH or even reduce the incidence of MASLD by maintaining homeostasis in the intestinal environment and the composition of the intestinal flora. Therefore, it is an effective target for the treatment of MASLD.

### 5.4. NLRP12 and MASLD

NLRP12 is a member of the NLR family expressed in bone marrow neutrophils, granulocytes, macrophages and dendritic cells, and it contains an N-terminal PYD structural domain, a central NACHT structural domain, and a C-terminal LRR. NLRP12 can induce the release of inflammasome-dependent cytokines IL-1β and IL-18 to protect against severe infections caused by pathogens infection, such as *Yersinia pestis* or *Plasmodium chabaudi*.

NLRP12 has been demonstrated to be a checkpoint for obesity that inhibits HFD diet-induced inflammation and maintain the production of short-chain fatty acids (SCFAs). Moreover, NLRP12 is an important regulator of beneficial bacteria such as *Lachnospiraceae*, and NLRP12 deficiency in HFD-fed mice lead to a decrease in *Lachnospiraceae* family members that caused obesity, inflammation, and metabolic dysregulation [186]. NLRP12 was also observed to play a role in reducing inflammation, and its expression was up-regulated in the early stages of liver regeneration and down-regulated in MASLD and acute and chronic liver injury [187]. NLRP12 binds to NF-κB-inducing kinase (NIK) and TRAF3, ultimately leading to the degradation of NIK and blocking downstream signaling events (Fig. 3).

The decrease in noncanonical NF-κB signaling leads to decreased expression of the chemokines CXCL12 and CXCL13 and reduced inflammation [188]. During HCC development, NLRP12 deficiency in mice significantly elevates the levels of pro-inflammatory cytokines and chemokines and activates the JNK signaling pathway, thus suggesting that NLRP12 probably inhibit the development of hepatic steatosis by regulating the JNK signaling pathway [189]. NLRP12 has show its potential ability involving the progression of MAFLD. However, the related studies of NLRP12 still be less.

## 6. RLRs

RLRs family includes retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 [190]. RLRs have been demonstrated to recognize dsRNAs in a wide range of cells, induce type I IFN production, and play a key role in enhancing the host clearance of viruses and immune surveillance [191]. The signaling mediated by RLR after recognition of viral genomic RNA is mainly dependent on the mitochondrial

antiviral signaling protein (MAVS) that is also known as IPS-1, VISA, or Cardif. In addition to their antiviral effects, RLRs play an important role in MASLD.

### 6.1. RIG-I and MASLD

RIG-I was the first member of this family. The N-terminus of RIG-I is a CARD region that binds to MAVS on the outer mitochondrial membrane and possesses signal transduction ability. The C-terminal portion of the repressor domain covers the CARD region in the unstained state and prevents the activation of the immune signaling pathway [192]. Moreover, the C-terminal structural domain (CTD) in the C-terminal domain can recognize specific viral RNAs, thus causing structural changes in the RIG-I molecule and exposing the CARD region that binds to MAVS and initiates the type I IFN signaling pathway. The proline-rich region in the middle region of the MAVS molecule binds to the downstream E3 ubiquitin ligase TRAF3 to further activate the downstream TBK/IKKi complex, ultimately leading to the phosphorylation and oligomerization of IRF3/7 and initiation of type I IFN expression [193].

Fatty acid toxicity is a major contributor to liver inflammation in patients with MASLD [194]. Autophagy is enhanced in the liver during the early stages of MASLD and is gradually suppressed as the disease progresses to the later stages. Studies have revealed that RIG-I activation increases autophagy to remove toxic lipid inclusion bodies, thereby inhibiting inflammation and apoptosis. RIG-I regulates autophagy by interacting with the autophagy receptor protein p62/SQSTM1, thus promoting LC3 cleavage and autophagy that in turn regulates the development of MASLD. Moreover, in a MASH mouse model, RIG-I expression was significantly reduced to suppress autophagy [195]. In the obese state, the inhibition of RIG-I activity by excess fatty acids attenuates the autophagic response, ultimately leading to increased lipotoxicity. RIG-I-induced autophagy contributes to alleviating the progression of MASLD [195] (Fig. 4).

However, a recent study has demonstrated that hepatocyte-specific RIG-I deficiency suppresses MASH-induced hepatocarcinogenesis. This study indicated that RIG-I expression was increased by HFD that enhanced cholesterol synthesis and steatosis, MASH, and MASH-induced hepatocarcinogenesis. JMJD4-demethylates RIG-I at K18 and K146 to prevent necroinflammation and MASH-induced hepatocarcinogenesis [196] (Fig. 4).

In summary, RIG-I is a potential target for treatment of MASLD. Although there are different experimental results, RIG-I that is demethylated at K18 and K146 probably exhibit valuable application for reducing MASH-induced hepatocarcinogenesis. However, few experimental and clinical studies examining RIG-I have been conducted and more studies are required.

### 6.2. MDA5 and MASLD

MDA5, also known as IFIH1, is a sensor of intracellular double-stranded dsRNA viruses [197]. MDA5 consists of an N-terminal CARD region, a central DExD/H motif helicase domain, and a CTD [198]. In addition to its classical role in antiviral defence, MDA5 has been reported to be involved in metabolic and immune diseases [197].

MDA5 is an important inhibitory factor in MASH, and it was observed that MDA5 was significantly downregulated in the livers of patients with MASH and mouse models. MDA5 overexpression significantly inhibited FFA-induced lipid accumulation and inflammatory responses in hepatocytes *in vitro,* whereas MDA5 downregulation promoted hepatocyte steatotoxicity. In hepatocyte-specific MDA5 knockout mice, HFD diet-induced hepatic steatosis, inflammation, and fibrosis were significantly exacerbated, and this could be reversed by MDA5 overexpression [199]. In this stduy, MDA5 significantly inhibited the activation of the apoptosis signal-regulated kinase I (ASK1)-MAPK pathway, whereas MDA5 deficiency enhanced its activation. MDA5 interacts with ASK1 and blocks ASK1 dimerization, inhibits

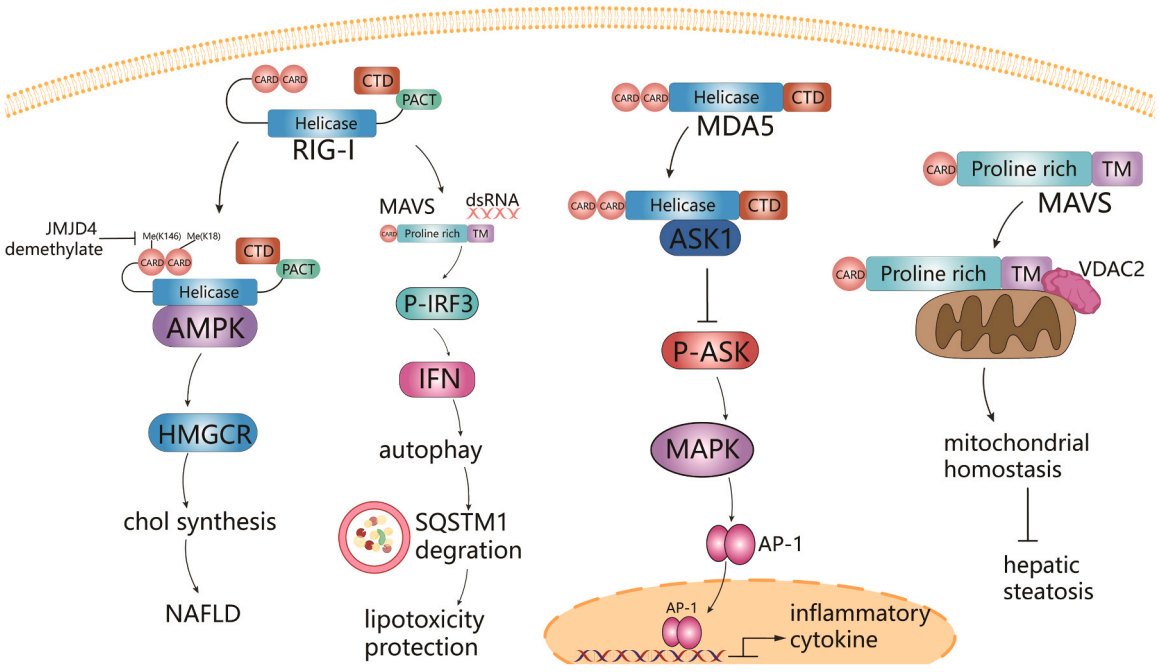


**Fig. 4.** The role of RIG-I, MDA5, and MAVS in the pathogenesis of MASLD. RIG-I can cause the activation of AMPKα to inhibit HMGCR phosphorylation, thus promoting HMGCR enzymatic activity and cholesterol synthesis which promoted MASLD. Demethylase JMJD4 can mediate RIG-I demethylation suppressed RIG-I signaling which restrained MASLD. In addition, RIG-I can advance MAVS activation which caused the increase in p-IRF3 activation, which further promoted the interferon signaling and this in turn activates autophagy. RIG-I regulates SQSTM1 in selective autophagy to prevent SQSTM1 accumulation leading to lipotoxicity. MDA5 directly interacted with ASK1 and suppressed its phosphorylation, which could promote MAPK signaling pathway, thus promoting the occurrence and development of MASH. MAVS interacts with the N-terminal stretch of voltage-dependent anion channel 2 (VDAC2) that mediates the downstream effects of MAVS in maintaining mitochondrial homeostasis in hepatocytes during metabolic stress, thus inhibiting the occurrence of MASH.

ASK1-JNK/p38 activation, and effectively suppresses hepatic lipid accumulation and metabolic disorders [199] (Fig. 4).

However, in another study, MDA5 expression was significantly increased in the livers of mice following a choline-amino acid high-fat diet induced model, and MDA5-positive macrophages were also detected in the livers of human MASLD, which exacerbate hepatic inflammation [200]. Moreover, LPS and TNF-α can upregulate the expression of MDA5, and macrophages with high expression of MDA5 may exacerbate hepatic inflammation [200].

In summary, MDA5 is a promising therapeutic target in MASH. Although MDA5 is involved in lipid metabolic processes in the liver, the role of MDA5 in liver inflammation induced by different models remains controversial and requires further study.

### 6.3. MAVS and MASLD

MAVS is a signaling adaptor on the outer mitochondrial membrane and a key protein in host defense against viral infections [201]. As a mediator between the immune response and metabolic regulation, MAVS can regulate glycolysis by interacting with hexokinases to maintain its mitochondrial localization and activation in the cell [191, 202]. MAVS possesses an N-terminal CARD region that mediates binding to RLR and a C-terminal transmembrane domain that anchors it to the outer mitochondrial membrane [191], and these are important for its function. MAVS protein expression was significantly downregulated in the livers of MASLD mice. The inability to induce type I IFN production by dsRNA stimulation is due to impaired MAVS separation from mitochondria and oligomerization in the liver of steatohepatitis [203].

Mitochondrial dysfunction is an important factor in MASLD development. In HFD diet-induced MASLD, MAVS deficiency triggers mitochondrial dysfunction during MASLD onset, ultimately leading to impaired mitochondrial respiratory capacity and membrane potential thereby causing metabolic disorders. In mouse primary hepatocytes, overexpression of MAVS reduces lipid accumulation induced by oleic acid [204]. Mechanistically, MAVS can interact with the N-terminal stretch of the voltage-dependent anion channel 2 (VDAC2) for maintaining mitochondrial function and inhibiting hepatic steatosis. These findings provide new insights into the metabolism of conventional immunomodulators. Targeting of MAVS may represent an avenue for the treatment of MASLD [204] (Fig. 4).

In conclusion, the association of MAVS and mitochondrial damage plays important roles in MASLD. The MAVS protein can inhibit lipid accumulation in hepatocytes and reduce ovrall lipid accumulation, and this represents an important target for MASLD. However, MAVS-signaling related drugs still wait for development.

## 7. DNA receptors

### 7.1. cGAS-STING and MALSD

Stimulator of interferon genes (STING), also known as transmembrane protein 173, is a cytoplasmic DNA sensor that can be activated by upstream cyclic dinucleotides. STING consists of an N-terminal structural domain spanning the ER membrane, a cytoplasmic region containing a ligand-binding structural domain, and a C-terminal tail [205]. In the presence of cellular DNA damage caused by viruses or other pathogenic factors, damaged DNA induces conformational changes in cyclic GMP-AMP synthase (cGAS) and catalyzes the production of cyclic GMP-AMP (cGAMP). cGAMP serves as a second messenger to recruit effector protein such as STING, that is located in the ER and facilitates the transport of STING from the ER to the perinuclear nucleus via the Golgi apparatus.

As a key effector protein of the pathway, STING promotes the activation of TBK1 phosphorylation and thus promotes the activation and translocation of IRF3 to produce IFNs. Meanwhile, STING activates IKK that phosphorylates the serine of the IκB subunit of the intracellular NF-κB-IκB complex for degradation, thereby releasing NF-κB dimers into the nucleus, initiating transcription, promoting secretion of inflammatory factors, and exerting pro-inflammatory effects [206].

Studies have revealed that the cGAS-STING signaling pathway is involved in the pathology of hepatitis, MASLD, liver injury and HCC [207,208]. STING expression is increased in the liver tissues of patients with MASLD. Moreover, hepatic mitochondrial function is abnormal in patients with MASH that exhibit significantly increased cytoplasmic mtDNA contents [209]. When hepatic phagocytes engulf apoptotic or dead hepatocytes, their DNA can enter the cytoplasm and activates the cGAS-STING pathway [210].

Similarly, STING levels were increased in the liver tissues of MASLD mice with HFD-induced steatosis. In a mouse model of HFD diet-induced steatosis, STING promoted macrophage-mediated hepatic inflammation and fibrosis in mice, but STING deletion in macrophages attenuated the severity of hepatic fibrosis and the inflammatory responses [207]. STING is also involved in glycolipid metabolic processes. Mice without STING expression exhibited reduced hepatic fat, inflammation, and fibrosis, thus suggesting that STING activation may promote hepatic lipogenesis and inflammation after fed with high fructose [211]. Furthermore, excessive lipid deposition in the liver of patients with MASLD leads to oxidative stress damage in the ER, thus activating the STING-TBK1 pathway and promoting hepatic inflammation [124].

Mechanistically, STING is involved in the activation of mitochondrial apoptotic pathway via Bax, ultimately resulting in liver inflammation and MASLD [212]. Additionally, activation of STING in monocyte macrophages and hepatic KCs promoted phosphorylation of TBK1, JNK and NF-κB that leads to the production of transforming growth factor-α (TGF-α) and IL-1β, and the production of these cytokines triggers the hepatocyte inflammatory pathway and produces TGF-β1. This induces the activation of HSCs, results in fibrosis, and ultimately leads to MASH development and even further cirrhosis and HCC [213, 214]. Recent studies have shown that mitochondrial division inhibitor 1 (Mdivi-1) effectively alleviated cecal ligation and puncture-induced liver injury partially through inhibiting STING signaling activation in KCs [215] (Fig. 5).

In summary, the STING signaling pathway is involved in pathological processes such as hepatic steatosis, hepatic fibrosis, and HCC, and STING causes hepatocyte apoptosis and upregulates the inflammatory pathway through impaired ER oxidative stress as well as the mitochondrial apoptotic pathway. This ultimately exacerbates the development of MASLD. Inhibiting STING has shown promise in treating inflammatory diseases, offering potential new avenues for NAFLD treatment [216]. C-176 is a furan derivative that inhibits the activation of the STING pathway and exerts anti-inflammatory effects [217]. However, this inhibitor has not been used in MASLD models, and therefore, further studies are warranted. Although STING agonists or inhibitors have demonstrated encouraging results in treating MASLD, there are still some deficiencies to be further studied. Moreover, research on the pathological mechanisms of the STING signaling pathway in NAFLD is still not comprehensive and needs further improvement.

### 7.2. AIM2 and MASLD

Melanoma 2 (AIM2) belongs to the HIN-200 structural domain protein family of IFN-inducible genes, and structurally it consists of an N-terminal PYD and a C-terminal oligonucleotide-bound HIN structural domain. It can be activated by double-stranded DNA or RNA, and activation of AIM2 can recruit ASC and pro-caspase-1 to form an inflammasome ~~to~~ and promote the maturation and secretion of IL-1α and IL-18.

AIM2 is involved in the development of hepatic steatosis and MASH. Studies have revealed that the activation of the AIM2 inflammasome contributes to the progression of steatosis to MASH in mice [88,218]. AIM2 also recognizes dsDNA released by damaged host cells and initiates the assembly of the AIM2 inflammasome complex, and this leads to

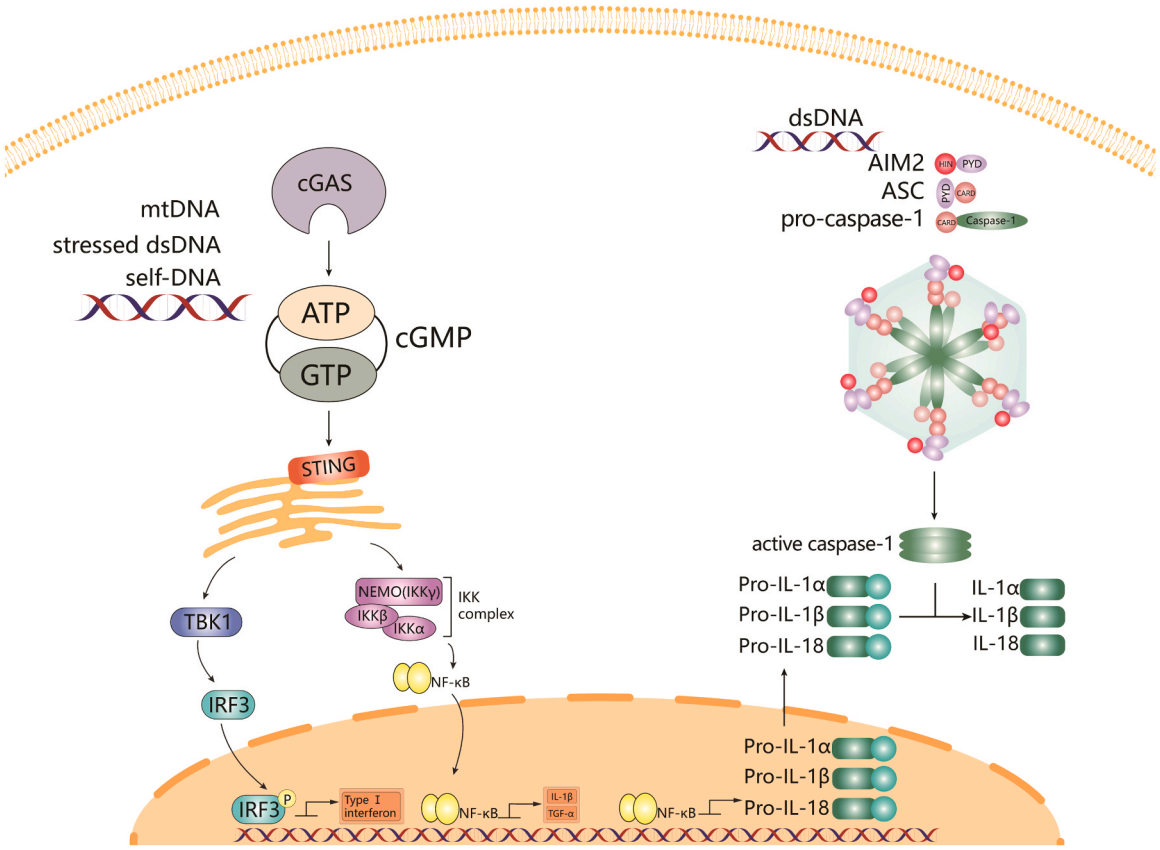


**Fig. 5.** The role of cGAS-STING and AIM2 signaling pathway in the progression of MASLD. The schematic detailing cytosolic mtDNA and dsDNA, which occur through pathogen infection, tumor cells, death cells or cellular stress, can be recognized by cGAS. Enzymatic activation of cGAS results in the synthesis of 2′-3′ cGAMP. The binding of cGAMP enables STING translocation from ER membrane to Golgi, then recruits TBK1 and IKK complex. The phosphorylation of IRF3 and NF-κB by TBK1 and IKK enable these transcription factor dimerization and translocation to the nucleus to induce gene expression of several cytokines, type I interferons, and chemokines. The schematic detailing cytosolic dsDNA, can be recognized by AIM2, HFD- and FFA-induced oxidative stressand mitochondrial damage which promote dsDNA release , promote AIM2 inflammasome activation, and the release of IL-18 and IL-1β.

the oligomerization of ASCs and the recruitment of pre-caspase-1 and the release of inflammatory factors IL-1β and IL-18 that in turn drive the development of MASLD [219,220] (Fig. 5). Moreover, in an MCD-induced MASLD/MASH mouse model, steatosis and steatohepatitis were associated with the upregulation and activation of AIM2 [88]. Furthermore, overexpression of the AIM2 in mice exacerbated HFD-induced MASLD, promoted inflammatory cell infiltration, and increased the expression of inflammation-related genes (IL-1β and IL-18). Conversely, down-regulation of AIM2 resulted in attenuation of MASLD symptoms and down-regulation of IL-1α and IL-18 expression [221]. The up-regulation and activation of AIM2 is dependent on MyD88 [88], and growth differentiation factor 15 can directly or indirectly inhibit the activation of AIM2 inflammatory vesicles to thereby prevent hepatic steatosis [222]. Besides, AIM2-deficient aged mice exhibited heightened lipid accumulation and hepatic triglycerides in comparison to their wild-type counterparts [223].

In summary, AIM2 is involved in the development of hepatic steatosis and MASH. AIM2 aggravates the development of MASLD by promoting the production of inflammatory factors and the infiltration of inflammatory cells. Therefore, reducing the infiltration of inflammatory cells in the liver due to the activation of AIM2 is an important approach for the treatment of MASLD.

## 8. Interplay of different PRRs in MASLD

PRRs coordinately interact with each other in the development of MASLD. A better understanding of molecular mechanisms underlying these interactions is very important for drug development. TLR2 deficiency resulted in altered expression of CD-14, a co-receptor of TLR4, and enhanced TLR4 signaling in TLR2-deficient mice feeding on HFD diet [71]. MDA5 positively regulates the TLR4 signaling pathway and TNF-α-mediated immune responses and exacerbates TLR4-mediated hepatic inflammation in monocyte-derived macrophages [224]. In MASLD, TLR4 exacerbates hepatic inflammation and cell death by binding to HMGB1 that then activates the NLRP3 inflammasome [37]. Moreover, the TLR4 signaling pathway increases the expression of NF-κB signaling to promote increased synthesis of NLRP3, and this exacerbates MASLD [225]. The TLR2 ligand can also increase NLRP3 expression in Kupffer cells but not in HSCs [78]. STING and TLR9 cooperate to exacerbate mtDNA-induced MASLD [226]. In addition to mutual cooperation, PRRs can inhibit each other to execute their function. NLRP6 can specifically negatively regulate LPS/TLR4-induced NF-κB and MAPK activity, inhibit deleterious inflammatory responses, and ameliorate the pathological process of MASLD [183].

### 8.1. PRRs signaling-related downstream pro-inflammatory cytokines

The interplay of PRRs signaling-related downstream pro-inflammatory cytokines (primarily TNF, IL-1, IL-6, IL-11, IL-18) also plays an important role in the evelopment of MASLD [227]. These cytokines have been demonstrated to be highly expressed in MASH. TNF was one of the first cytokines to be investigated, and its expression was correlated with the degree of inflammation in MASH [228]. Antibodies aganist TNF inhibit inflammatory activity and improve MASLD in mice [228]. The TNF-α inhibitor of etanercept as a clinical drug has been demonstrated more efficacious in regard to reducing the risk of

developing hepatic fibrosis compared to that of Psoralen and UVA therapy, and this preventive effect could be related to its anti-inflammatory and glucose homeostatic properties [229]. However, the patients gained significant weight with increases in anthropometric measurements and BMI during treatment and these changes themselves may represent risk factors for the development of hepatic fibrosis in patients with MASLD [230]. This issue must be further addressed.

IL-1 type cytokines mediate key features of MASLD, including hepatic steatosis, inflammatory infiltrates, fibrosis, IR, and adipose tissue inflammation. Members of the IL-1 family have been demonstrated to affect insulin-glucose metabolism and regulate metabolic dysfunction in patients with MASLD, and IL-1α deficiency and IL-1β deficiency mice are hepatoprotective against diet-induced steatosis and exhibit reduced expression of fibrosis-associated genes [231]. Several preclinical studies have convincingly revealed the crucial role of IL-1 type cytokines in MASLD. IL-1R3 has been recently demonstrated to be the co-receptor in various signaling pathways involving six cytokines of the IL-1 family (IL-1α, IL-1β, IL-33, IL-36α, IL-36β, and IL-36γ). The IL-1R3 antibody (MAB-mR3) significantly attenuates heterogeneous cytokine-driven inflammation and disease severity and is a therapeutic option with considerable translational benefits [232]. A monoclonal antibody of IL-1β, canakinumab, has been demonstrated to improve metabolic inflammation and protect against non-fatal myocardial infarction and stroke, but it exerted no effect on serum low-density and high-density lipoprotein levels in clinical studies (NCT01327846). Further clinical studies examining the effects of canakinumab on inflammation and cardiovascular risk are ongoing (NCT02272946). However, no data regarding hepatic steatosis are available from clinical trials to determin if canakinumab affects MASLD in humans. Therefore, clinical studies targeting the role of IL-1 cytokines in MASLD treatment are urgently required.

IL-6 is another potent pro-inflammatory cytokine, and its concentration in both liver and adipose tissue of patients with MASLD is increased [233]. In the liver, studies have highlighted that chronic exposure to IL-6 promotes hepatic gluconeogenesis and hepatic IR. Administration of rIL-6 may contribute to the aggravation of fatty liver disease through increasing lipogenesis [234]. However, in a mouse model of diet-induced MASH, blocking of IL-6 signaling with anti-IL-6Rα enhances steatosis but reduces signs of inflammation [235]. HFD-fed IL-6 KO mice exhibited worse liver injury and fibrosis but less inflammation than did wild-type mice. Moreover, hepatocyte-specific Il-6Rα KO mice exhibited more steatosis and liver injury, and myeloid-specific Il-6Rα KO mice exhibited greater liver fibrosis than did WT mice [236]. The IL-6 family of cytokines is characterized by the common use of the signal-transducing receptor chain glycoprotein 130 (gp130). The newly engineered gp130 cytokine IC7Fc has demonstrated promising preclinical results for the treatment of type 2 diabetes, obesity, and liver steatosis [237]. A deeper understanding of the main roles of the IL-6 family of cytokines under homeostatic and pathological conditions, their signaling pathways, sources of production and target cells is crucial for the development of improved treatments.

IL-11, a member of the IL-6 family, is upregulated in various fibro-inflammatory diseases and MASH. In an animal model of MASLD, the blockade of the pro-inflammatory cytokines by the administration of anti-IL-11 or anti-IL-11-RA antibodies attenuated hepatic steatosis, hepatic inflammation, and fibrosis [238]. These neutralizing antibodies improved the cardiometabolic profile of mice and may be useful for the treatment of MASH in the future.

IL-18 is primarily produced by macrophages in the liver and can activate NK cells via the Fas ligand (FasL) pathway to promote apoptosis of infected or damaged hepatocytes, ultimately leading to massive hepatocyte death [239]. In a clinical study, higher IL-18 levels were significantly associated with chronic liver disease and were also associated with increased liver injury markers and portal fibrosis in obese subjects with MASLD, as well as with plasma concentrations of liver injury markers in healthy subjects [240]. In addition, IL-18 and IL-18/IL-18BP ratios are significantly elevated in patients with MASLD compared to those in healthy controls [241]. Excessive IL-18 is harmful to the liver, and LPS-induced liver injury can be prvented by treatment with a neutralizing anti-IL-18 antibody [242].

### 8.2. The interplay of PRR on gut microbial balance

Multiple PRRs have recently emerged as important steady-state sensors and regulators of the intestinal microbiota, and the innate immune system not only defends against invading pathogens but also shapes commensal microbial communities. Disruption of these receptors may alter the gut microbial composition, and this subseuently affects host metabolic homeostasis.

In this regard, mice deficient for TLR1, TLR2, TLR4, TLR5, Dectin-1, NOD2, NLRP6, and NLRP12 have recently been demonstrated to develop aberrant gut microbial communities and are predisposed to MASLD (Table 2). These metabolic phenotypes can be reproduced by using microbiota transplantation and can be reversed by antibiotics, thereby establishing a causal role of the microbiota in the development of metabolic disorders. Once the gut microbial balance disrupted, increased endotoxemia causes dysbiosis that increases the influx of agonists of PRRs into the portal circulation. In particular, the diet (particularly HFD) has emerged in recent years as one of the most factor triggers for impairing gut microbiota composition and endotoxemia with an impaired intestinal barrier. The damages constitute an important prerequisite for the translocation of potentially harmful bacteria and their effector molecules PAMPs to the liver. The PRRs that are expressed in the liver open a cooperative effect on the progression of MASLD in regulating inflammatory events.

## 9. Conclusion and outlook

The innate immune system possesses multiple recognition mechanisms in different cell types and subcellular structures, and each PRR signaling pathway plays an indispensable role in the elimination of pathogens and the maintenance of immune tolerance. PRRs activate the

**Table 2**
The correlation of PRRs with the gut microbiota.

| PRRs | Type of gut microbiota | Correlation |
|---|---|---|
| TLR1 | Beneficial bacteria, Gemmiger,Ruminococcus genera | Negatively [95] |
| | Hazardous bacteria Holdemanella genus | Positively [95] |
| TLR2 | Beneficialbacteria Akkermansiamuciniphila | Negatively [72] |
| | Hazardous bacteria E. coli NF73–1 | Positively [250] |
| TLR4 | Beneficialbacteria Lactobacillus,Muribaculaceae, acidophilus, Bifidobacteriuminfantis, Firmicutes,Fusobacteriota, Bacteroidetes, Proteobacteria, Cyanobacteria, Unclassified, Clostridium, Sutterella, Candidatus, Arthromitus, Bacteroides,Parabacteroide | Negatively [251–254] |
| | Hazardous bacteria Faecalibaculum,Colidextribacter, Verrucomicrobiota,Bifidobacterium, Anaeroplasma, Oscillospira, Helicobacter Odoribacter | Positively [251, 253,254] |
| TLR5 | Hazardous bacteria Escherichia coli | Positively [105] Negatively [106] |
| NOD2 | Beneficialbacteria Erysipelotrichaceae | Positively [136] |
| | Hazardous bacteria Clostridiales | Negatively [136] |
| NLRP6 | Beneficialbacteria Akkermansiamuciniphila | Positively [183, 184] |
| NLRP12 | Beneficialbacteria Lachnospiraceae | Positively [186] |

intrinsic immune defence response after being recognized by the corresponding PAMPs by participating in and promoting inflammatory response through the secretion of a variety of cytokines. PRR signaling has become a hot research topic, as it represents an important target for inflammation and lipid metabolism-related diseases.

With the elucidation structures of PRRs and signal transduction processes and functions, future studies may expand our understanding of how PRRs interact with obesity-induced inflammatory pathways, benefiting the clarification of pathogenesis of MASLD. The PRR is involved in the development of MASLD through multiple mechanisms. Products of the intestinal microbiota and danger signals from damaged hepatocytes constitute key PRR ligands that promote MASLD. PRRs signaling, gut microbial composition, ER stress and mitochondrial dysfunction synergistically regulate inflammation, and this may exert an important influence on the development of MASLD.

Overall, the molecular mechanisms of PRR are complex, and it is urgent to better understand the interactions among PRR signaling, microbial composition, organelles, and immune cells in MASLD to lay the basic framework for the treatment of MASLD. The design of drugs targeting the PRR signaling system to modulate the immune function of the body will require a broad scope of development in the treatment and prevention of MASLD. Currently, there are a number of remarkable findings regarding PRR-targeted drug development and preventive therapy for MASLD (Table 1). However, the adverse effects associated with drug therapy should not be underestimated. Therefore, determining how to intervene in the pathogenesis of MASLD and prevent side effects are the keys to treatment, and this will require more efforts.

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## CRediT authorship contribution statement

**Liping Han:** Visualization, Validation. **Dan Su:** Visualization, Validation. **Yaoxin Li:** Software. **Feifei Gao:** Writing – original draft, Investigation. **Zhiwei Feng:** Supervision, Funding acquisition. **Xuehan Zhang:** Visualization, Validation. **Yueming Li:** Software. **Lili Yu:** Writing – review & editing, Project administration, Funding acquisition.

## Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Data Availability

No data was used for the research described in the article.

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